CRYSTAL METHAMPHETAMINE

THE SILENT EPIDEMIC

DATA PACKET

PREPARED BY

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Document Objective

While opiate deaths are being addressed by new drugs such as the first non narcotic non drug substitution medication Lucemyrarug which eliminates opiate withdrawal symptoms. There are no drugs to help curve Meth withdrawal symptoms which are largely psychological and take 18 to 24 months to resend as SSRI's (Serotonin reuptake inhibitors) and SNRI's (Serotonin Noreproeferine reuptake inhibitors) do not affect the dopamine system which Crystal meth destroys. There are two drug epidemics in this country yet only opiates are talked about. This document will outline information about Crystal meth in three major ways…….

1. **General information taken from research articles and research studies.**
2. **The Matrix model which is the best treatment we have for Crystal Meth**
3. **Research Articles which cite research studies.**
4. **Research Studies which which are the basis of information**

The reader may choose to read what to read based on the level of detail they wish to see.

My Story

Please visit the below you-tube video for my story. Since this video I have relapsed once and managed to get clean after nine months of being in active addiction. I want to break the Stereotype that a substance abuse user of Crystal math can be spotted a mile away. I used for 4 years without anyone knowing completing college and working a full time job as an engineer.

Search on Youtube - “**A Secret Diamond in my secret Life”**

Direct Link: Dirhttps://www.youtube.com/watch?v=qYhVbOcF0iw

Comparison of Crystal Methamphetamine to other Narcotics

There are two major classes of narcotics (Definition has changed over time), they are stimulants and depressants.

Stimulants	Depressants
Amphetamines (Synthetic) – Adderall, Ritalin, Meth, Crystal Meth	Alcohol
Cocaine / Crack (Plant Derived)	Opiates (Plant Derived) - Morphine Codine
Nicotine – Cigarettes	Opioid (Synthetic) - OxyContin, Hydrocodine, Heroin, Fentanyl
Caffeine - Coffee	Benzodiazepines (Xanax, Ativan, Valium)

How is Crystal Meth differs from Depressants?

The main difference besides the obvious one is a stimulant and one is a depressant is Crystal Meth actually changes how much the brain pumps out certain neurotransmitters. Most depressants mimic neurotransmitters. When a person stops taking a depressant the production of neurotransmitters are relatively unaffected. Within weeks the person brain is back to normal since the drug didn't cause the brain to produce more or less of a neurotransmitter. A stimulant will actually cause the brain to produce more or less of a neurotransmitter. When a person stops taking a stimulant the brain stops producing the neurotransmitters and it can require a lot of time for the person to feel normal again.

How is Crystal Meth Different then Cocaine?

Crystal Meth is in the same class as cocaine/crack. There is a lot of confusion in general of the differences between these two powerful stimulants

Crystal Methamphetamine	Cocaine / Crack
Raises dopamine levels (Euphoria) to 1400 dopamine units	Raises dopamine levels (Euphoria) to 400 dopamine units
Duration of action: 12 hours	Duration of action: 30 minutes
Synthetically Created (Man made)	Plant Derived (Naturally occurring)
Can be created in Meth labs in home in the United States	Imported from Latin America / Mexico
Cheap	Expensive

Facts about Crystal Meth

- **Like amphetamine, methamphetamine increases activity, decreases appetite and causes a general sense of well-being.** Amphetamine has been used for weight control, for athletic performance and endurance, for treating mild depression, and to help truckers complete their long hauls without falling asleep. Methamphetamine has been widely marketed to women for weight loss and to treat depression.
- **Increased or prolonged use of methamphetamine can cause sleeplessness, loss of appetite, increased blood pressure, paranoia, psychosis, aggression, disordered thinking, extreme mood swings and sometimes hallucinations.** Many users become physically rundown, which leaves them susceptible to illness. The discontinued use of methamphetamine by heavy users will create withdrawal symptoms, including severe depression, lethargy, anxiety and fearfulness. Such effects are less pronounced with oral use and in lower dosages.
- **Methamphetamine production is a relatively simple process, especially when compared to many other recreational drugs.** It is frequently reported on in the media when home meth-producing labs are busted.
- **Pharmaceutical methamphetamine is still available legally under the brand name Desoxyn, but only infrequently prescribed to treat severe obesity, narcolepsy and ADHD.** Pharmaceutical amphetamine is available by prescription under a number of brand names (most notably Adderall), while other amphetamine-like stimulant medications are also widely prescribed (such as Ritalin), and are commonly prescribed to treat narcolepsy, ADHD, fatigue and depression. Although ostensibly not available to enhance productivity or wakefulness, amphetamine is commonly used that way. This has created a divide between those with health insurance who are able to obtain stimulants through legal means, and those who seek out black-market stimulants and face arrest.
- **Contrary to a common misconception, mMethamphetamine is not “instantly addictive” for most people who use it.** Most people who use Methamphetamine do not develop an addiction. For those individuals who do develop an addiction, treatment for Methamphetamine addiction is similar to that for cocaine and other stimulants and just as likely to succeed.

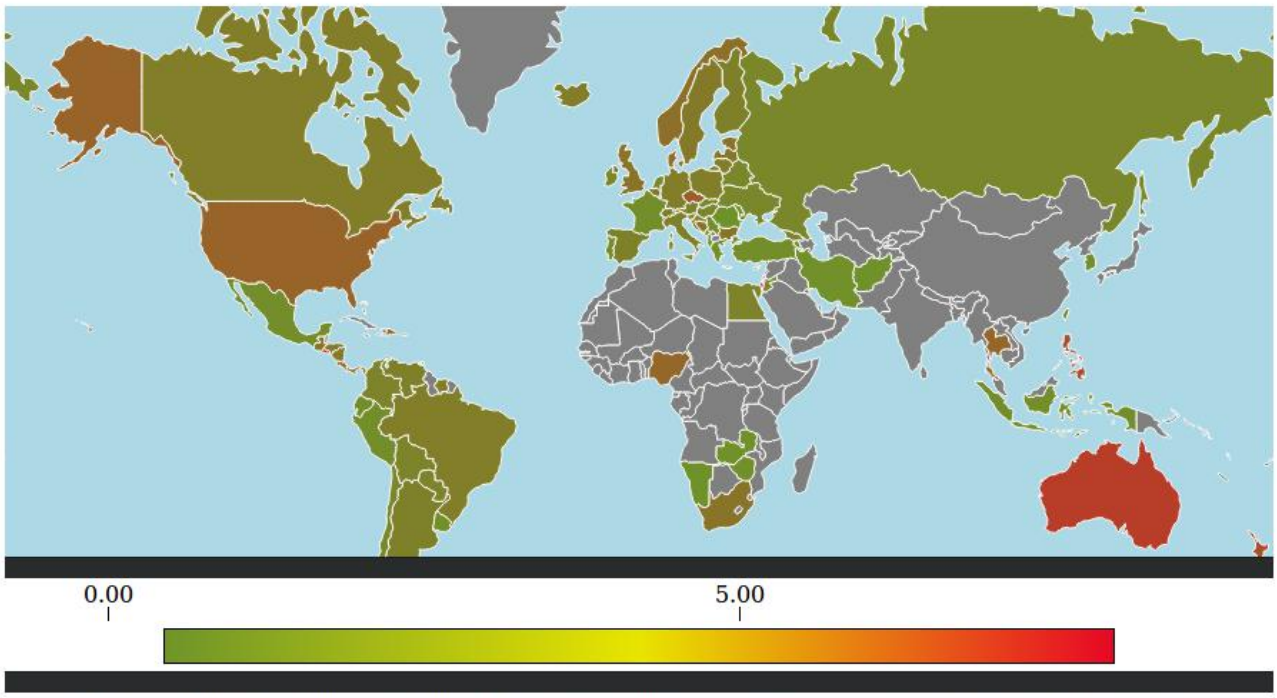
Crystal Meth Worldwide

Who's Abusing Methamphetamine?

Methamphetamine is a commonly viewed as a dangerous substance when used in non-medical situations. Despite the dangers, **use remains high in the US** and even higher overseas in Europe, Asia, and Australia.

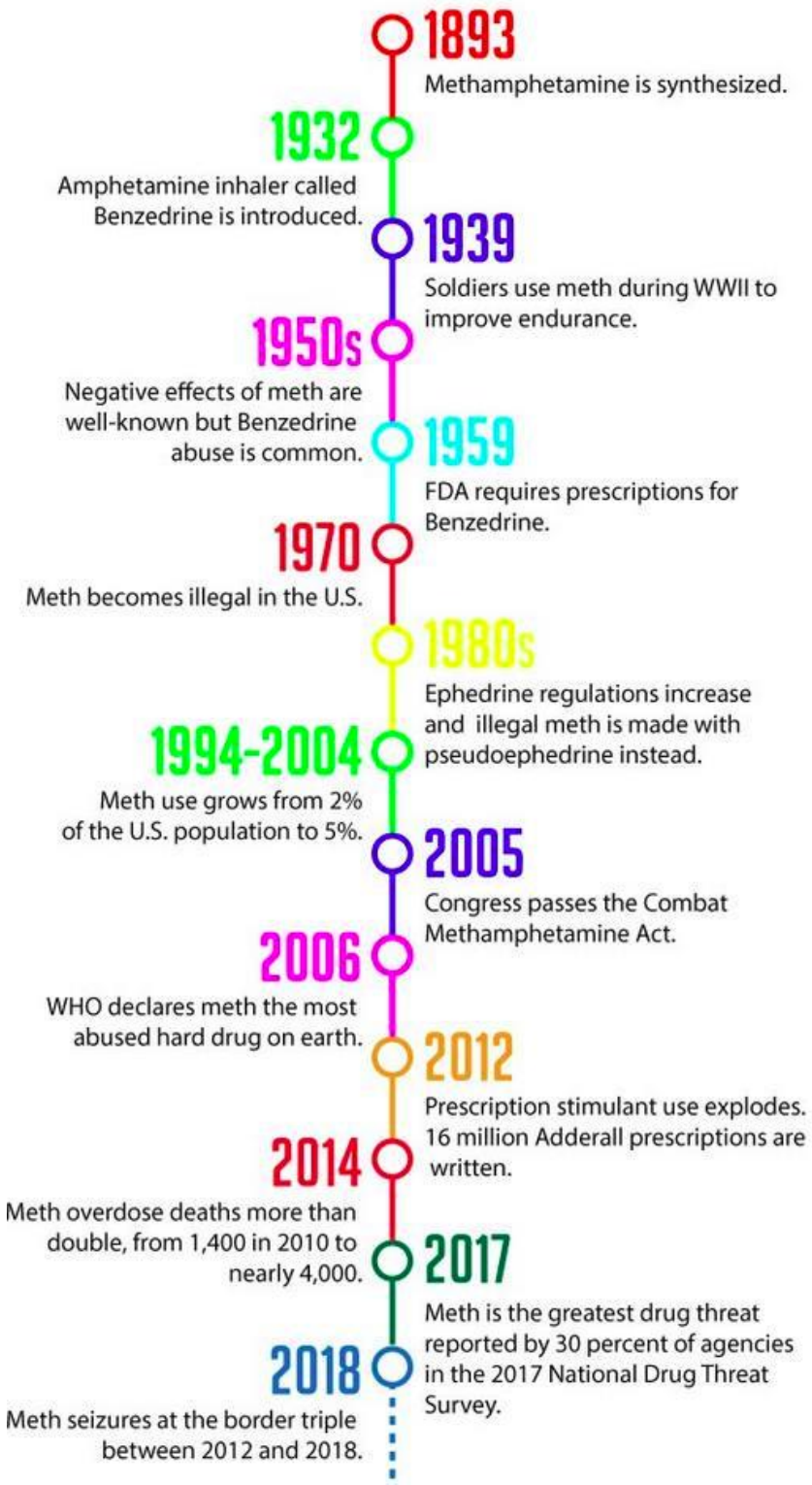
As many as half of people that seek drug treatment in the Czech Republic, Sweden, Finland, Slovakia, and Latvia seek it for addiction to methamphetamine.

Countries using the most amphetamines



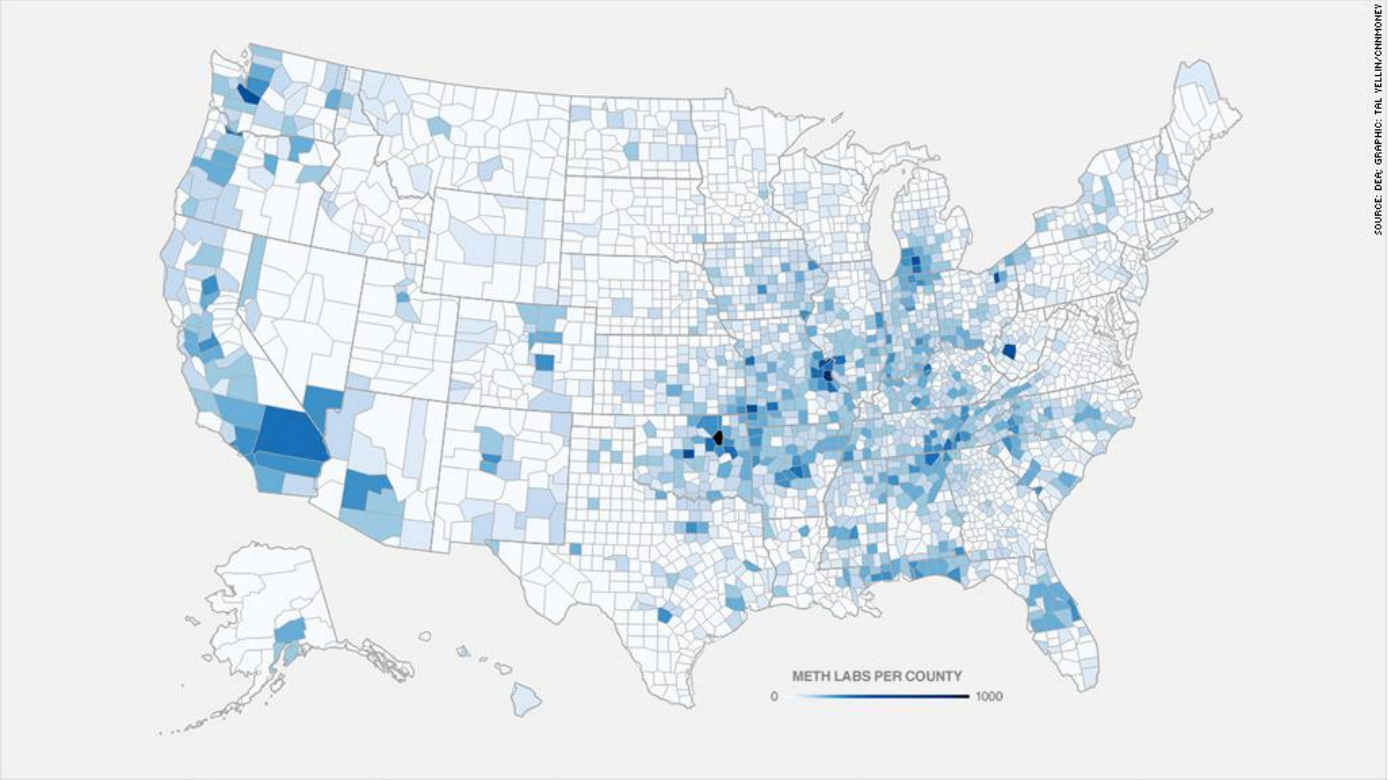
As the above graph illustrates, the people abusing methamphetamines come from every corner of the world, with higher concentrations of people in the Czech Republic, Australia, and the Philippines. It is interesting to note that Japan, the country that had very high levels of abuse following World War II, now has a lower abuse rate.

Crystal Meth History


1893
Methamphetamine is synthesized.
1932
Amphetamine inhaler called Benzedrine is introduced.
1939
Soldiers use meth during WWII to improve endurance.
1950s
Negative effects of meth are well-known but Benzedrine abuse is common.
1959
FDA requires prescriptions for Benzedrine.
1970
Meth becomes illegal in the U.S.
1980s
Ephedrine regulations increase and illegal meth is made with pseudoephedrine instead.
1994-2004
Meth use grows from 2% of the U.S. population to 5%.
2005
Congress passes the Combat Methamphetamine Act.
2006
WHO declares meth the most abused hard drug on earth.
2012
Prescription stimulant use explodes. 16 million Adderall prescriptions are written.
2014
Meth overdose deaths more than double, from 1,400 in 2010 to nearly 4,000.
2017
Meth is the greatest drug threat reported by 30 percent of agencies in the 2017 National Drug Threat Survey.
2018
Meth seizures at the border triple between 2012 and 2018.

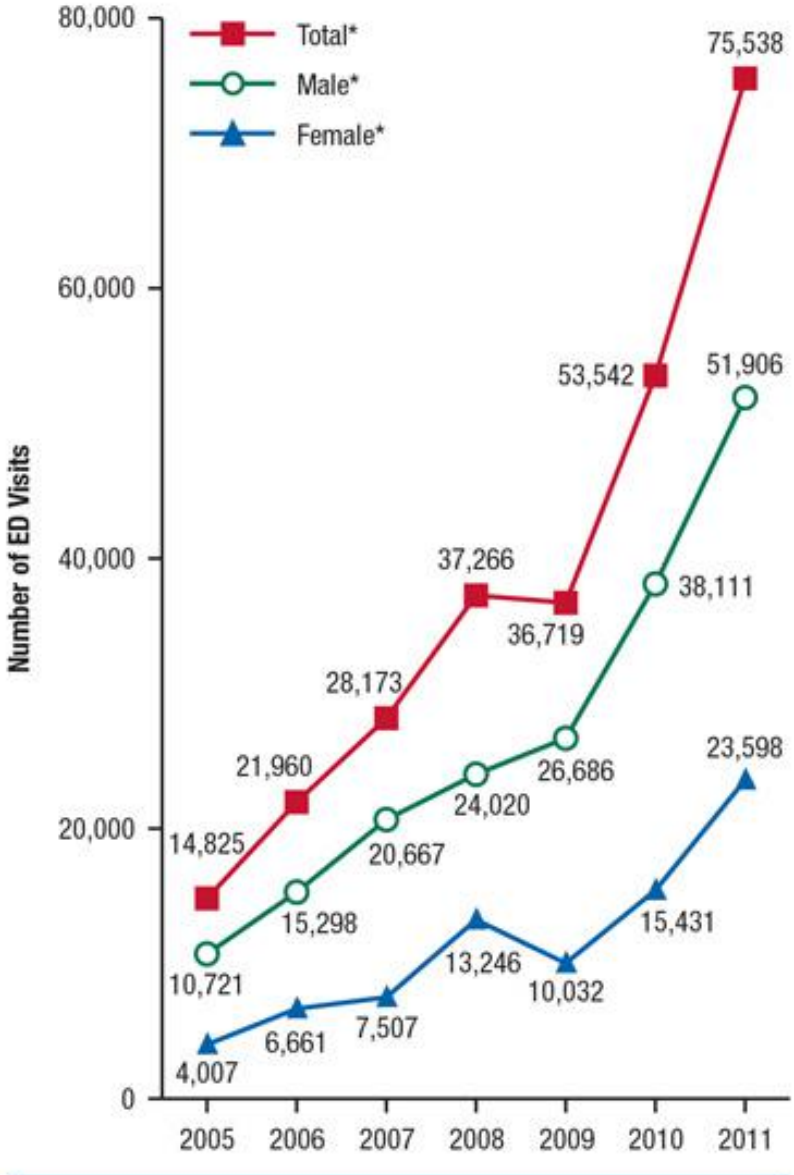
Meth Labs

Unlike other narcotics such as Opoids Cocaine Cystal Meth can be produced cheaply in homes or apartments. As border seizers increase more labs are popping up around the United States.



Meth Emergency Room Visits

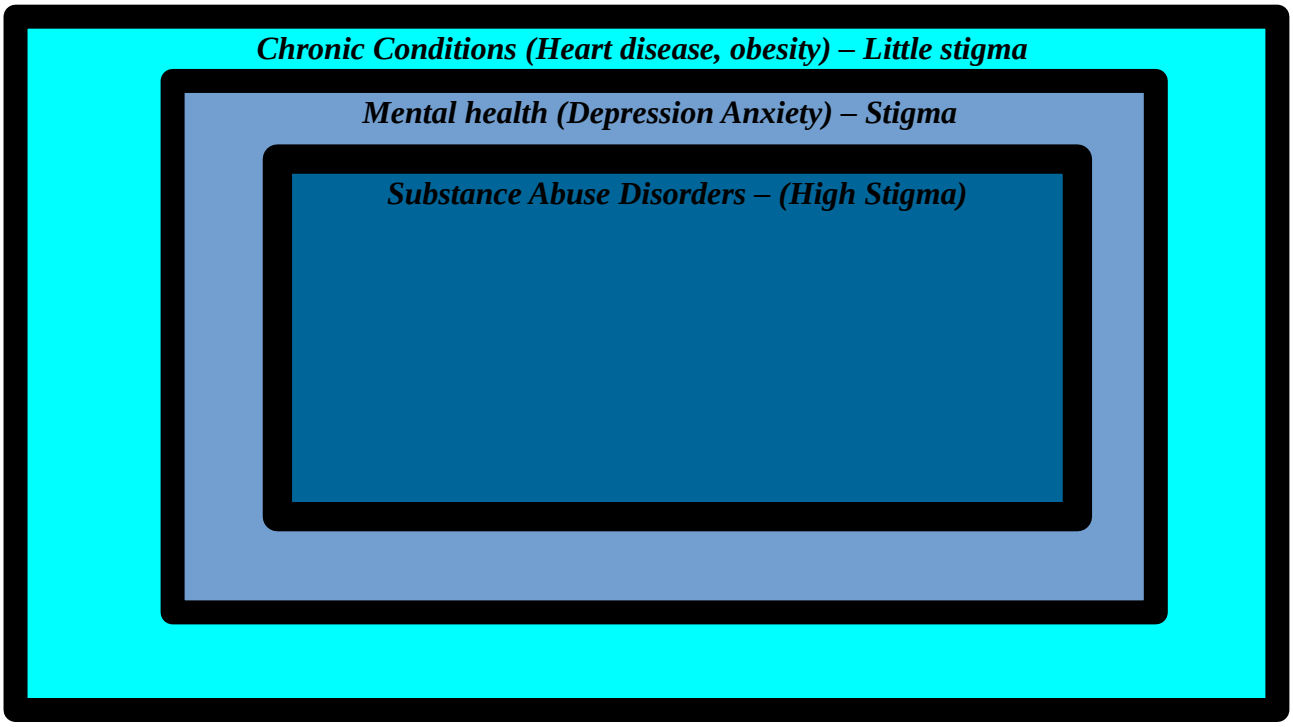
From what I have read Meth emergency visits are climbing exponentially in the past two decades. Unfortunately I was unable to find a visual as data is analyzed ever decade. The below graph shows the trend in the past decade. From what I have read this pattern is continuing to grow exponentially.



* The difference between 2005 and 2011 is statistically significant at the .05 level.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Meth Stigma


Chronic Conditions (Heart disease, obesity) – Little stigma
Mental health (Depression Anxiety) – Stigma
Substance Abuse Disorders – (High Stigma)

Stigma for a Meth user is high. Even in the drug community Meth is seen as a drug no one touches and if they do they are considered the worst users. Often times people deny their use in meetings and say they use other drugs. The next two sections explain hospital and insurance stigmas I have experienced when I tried to get into rehabs.

My Insurance Stigma and Meth Use

Medicaid Insurance usually will cover Rehab for Meth users at least in the state of MI presently in 2019. However I had private insurance and they did not cover Meth Rehab as they claim Meth is a psychological addictive and not physical addictive. Both times I tried to get into rehab initially denied and both times I had severe attempts on my life. Both times I went into rehab I had to lie and say I was using Heroin and because I was in hospitals before for suicide attempts I was able to go to rehab and pass a drug test and not get kicked out. This needs to change. All insurance should cover drug rehab despite the substance. I have had countless friends try to stop on their own and because of acute withdrawal are either dead by suicide or committed violent crimes and are in jails.

My Hospital Stigma and Meth Use

In 2018 I went to a hospital to try to detox off Meth and was not even admitted I was told by a hospital intake coordinator that there is no reason for me to be here and that there is nothing they can do unless I say I am going to kill my self. Due to my private insurance plan we could not afford another 5000 dollar bill for 3 weeks in a inpatient mental health setting. I needed to detox as they would detox a heroin addict. Studies show that Meth is just as hard to get off as heroin but because the person wont die from seizers insurance and hospitals wont help you but I have had countless friends take their own lives. Psychological withdrawal I just as bad a physical withdrawal. In both cases there is loss of life.

Treatment Methods for Crystal Meth

Pharmaceutical Approaches

******There are NO pharmaceutical drugs to help treat Crystal Meth Addiction*******

Unlike heroin where drug replacement or drug substitutions drugs are available such as Methadone, Saboxone, and Vivitrol, there are no approved substitutions for Crystal Meth. This is because giving a patient Adderall which is chemical similar to Crystal Meth will only prolong the repairing of the dopamine receptors. This is because other Narcotics Mimic Neurotransmitters and does not force the brain to produce Dopamine. Crystal Meth is the only drug that makes the Brain produce large amounts of Dopamine and because the duration of action is 12 hours this destroys the dopamine receptor.

Anti Depressants such as SSRI's and SNRI's Anti Consultants, Anti Psychotics have been well tested and none of them affect the Dopamine System. The drug Burprion (Wellbutrin) which does affect dopamine has shown some relief to the Dopamine system if the user only used periodically. (Once a month).

Non Pharmaceutical Approaches

Matrix Model

The United States research shows that treatment for ALL Narcotics are the same. However other countries where Crystal Meth is the main Narcotic they treat Crystal Meth Differently using the Matrix Model. While many rehabs across the United states CLAIM that they use the Matrix Model this is false and the two rehabs I have gone to have not either. The Matrix Model is more then a Cognitive Behavioral Therapy Approach which most if not all rehabs implement and claim they are implementing the Matrix Model when in reality they are only implementing part of the Matrix Model. The relapse rate for Crystal Meth is between 96% - 98% in the United States, while in Australia where the Matrix Model is implemented relapse rates are at 80%. WebMD only has posted the word Matrix model on their website as of March 2019.

Eight Principles of Matrix Model

1. Building a strong, respectful relationship between therapist and client.
2. Following through on the structure of the program and the expectations of the client.
3. Providing quality educational content to the client that explains the nature of substance use.
4. Using varied treatment approaches like CBT and motivational interviewing to meet the client's needs.
5. Rewarding and encouraging the desired behaviors while extinguishing the negative behaviors.
6. Engaging and educating the family about addiction and recovery.
7. Motivating members to participate in self-help and community-based programs in addition to the Matrix Model.
8. Checking for substance use with urine testing.

Meth Withdrawal – A Personal Account

Meth withdrawal falls into two categories

1. Acute Withdrawal – The first 7 days

2. Post Acute Withdrawal – 18 to 24 months out.

Acute Withdrawal

Meth Withdrawal affects individuals differently. However the documentation provided in the United States only shows that you get sleeply.

As a Meth user for 6 years I have seen three ways people withdrawal Meth

1. The sleepy user – Experiences no real affects they sleep eat and drink

2. The angry user – Person gets agitated and violent and will do anything from going through this.

3. The suicidal user – The user shuts down emotionally and just wants to die leading to a suicide attempt.

Post Acute Withdrawal

Meth Post Acute Withdrawal is characterized for a Meth user for the first 18 to 24 months until the brain is able to produce its own dopamine. From a personal account I characterize this period of three major things that cause relapses.

1. Meth Dreams – having Meth dreams every time you sleep even during longest times of sobriety meth dreams were a nightly thing. The vividness of this is unimaginable as I woke up thinking I got meth taking a look at my nightstand seeing if I actually got some. Or dreams of some of the things I did in my active addiction

2. Cravings – From what I have read your brain tries to produce dopamine and can not so the brain swells causes debilitating cravings that leave you laying there for hours in panic attacks and making you want me to use the drug more then anything.

3. Triggers – Things that can cause a craving. For me seeing rock salt on roads reminds of this and causes cravings. Seeing other people drink or smoke pot causes a cravings to insue.

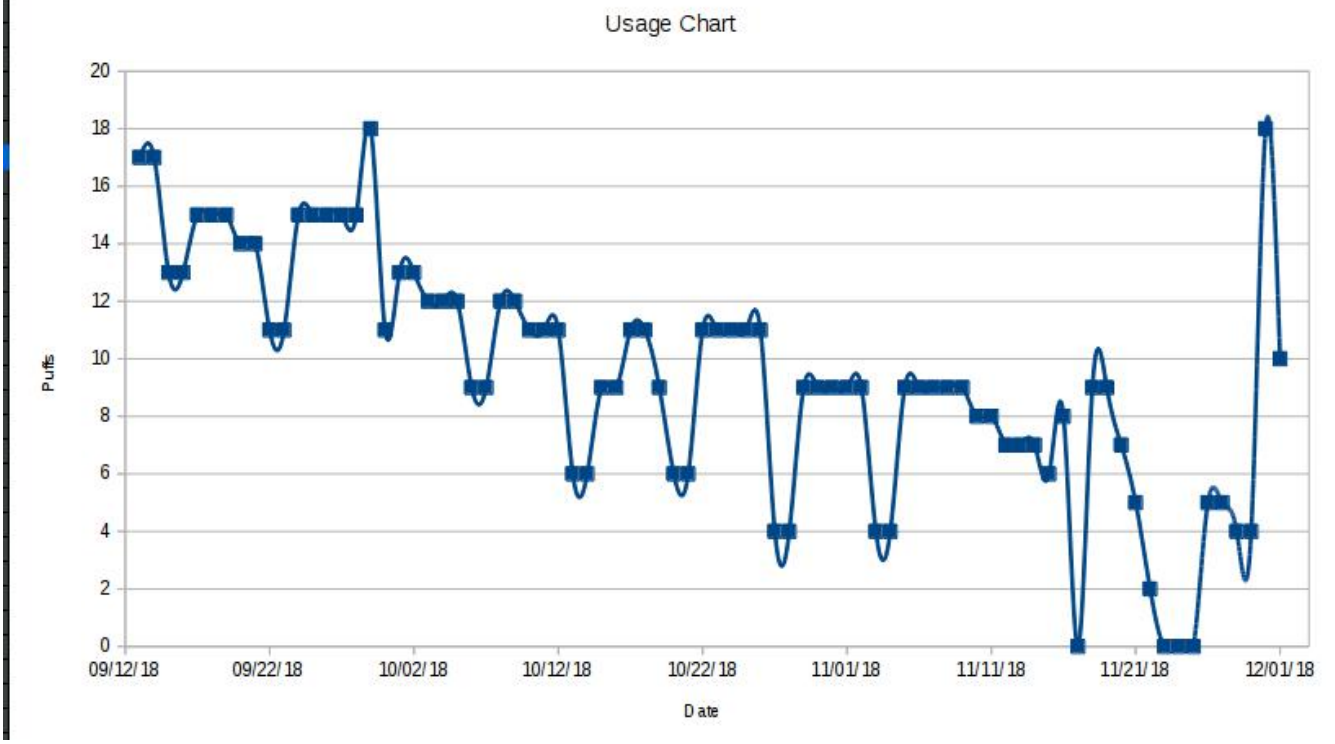
When you want to stop and cant – A personal Account

When I was using and couldnt stop and could not get into a rehab or detox at a hospital these are the things that helped me live day to day until the pain was great enough that I detoxed on my own with the help of family.

Track your use / Graph your use

This helped me see dangerous signs of when my use was increasing and decreasing.

11/13/18	Tuesday	7	0.16	4 meals	1 Pedalyites I 16 oz water	4	YES
11/14/18	Wednesday	7	0.16	2 meals	2 Pedalyites I 16 oz water	6	YES
11/15/18	Thursday	6	0.14	2 meals	2 Pedalyites I 8 oz water	6	NO
11/16/18	Friday	8	0.19	3 meals	hospital	4	NO
11/17/18	Saturday	0	0	1 meal	hospital	4	NO
11/18/18	Sunday	9	0.22	3 meals	2 Pedalyites I 16 oz water	8	NO
11/19/18	Monday	9	0.22	2 meals	1 Pedalyites I 16 oz water	8	NO
11/20/18	Tuesday	7	0.16	3 meals	1 Pedalyites I 32 oz water	6	NO
11/21/18	Wednesday	5	0.14	2 meals	1 Pedalyites I 16 oz water	6	NO
11/22/18	Thursday	2	0.05	3 meals	2 Pedalyites I 16 oz water	7	NO
11/23/18	Friday	0	0	2 meals	2 Pedalyites I 16 oz water	10	YES
11/24/18	Saturday	0	0	4 meals	2 Pedalyites I 16 oz water	12	YES
11/25/18	Sunday	0	0	2 meals	2 Pedalyites I 16 oz water	12	YES
11/26/18	Monday	5	0.14	3 meals	2 Pedalyites I 16 oz water	5	NO
11/27/18	Tuesday	5	0.14	3 meals	1 Pedalyites I 16 oz water	6	YES
11/28/18	Wednesday	4	0.12	2meals	1 Pedalyites I 16 oz water	6	YES
11/29/18	Thursday	4	0.12	2 meals	0 Pedalyites I 32 oz water	5	YES
11/30/18	Friday	18	0.4	2 meals	0 Pedalyites I 16 oz water	2	NO
12/01/18	Saturday	10	0.24	2 meals	0 Pedalyites I 16 oz water	4	NO



Tell your Doctors

Tell your primary care doctor about your use. If they are not receptive get another primary care doctor. When I relapsed I wrote my doctor a letter. Get a psychiatrist. Try different drugs who knows maybe an SSRI will work for you. I worked with a psychiatrist to when to a low enough use to where I could get off of it completely without having a suicide attempt.

Example:

Dr [redacted]

Hello this is Ryan [redacted]. I called for an appointment but you didn't have availability until December 5th. I wanted to give an update of my care and what I am doing about my relapse on meth as you have been a part of my recovery and support.

Due to the issue of my insurance not allowing me to go to inpatient rehab since they wont cover inpatient for Meth since its psychologically addictive and not physically addictive. I spoke with Courtney on my chart she offered to help, but my therapist is looking into it. I have a new therapist and psychiatrist who are going to work with me on weening me off. Enclosed is my usage chart from when I start tracking my use. The psychiatrist is working with me to be completely off meth in a months time. She has prescribed me Bupropion (150mg) which is suppose to help raise dopamine and Risperdal (.5 mg) to help the anxiety and severe depression I get when I get off of it. Since of what happened the past two times I just stopped cold turkey I decided to try this weening off approach under her care.

I appreciate you taking the time reading this and I hope this plan will work. Below is my new therapist and psychiatrist information. I have also updated my medications on my chart.

Thank you,
Ryan [redacted]

Therapist:
[redacted]

Psychiatrist

[redacted]

Educate Your Self

Educate your self about Meth. There is so much information out there. Find out if your insurance covers rehabs. Find out if you qualify for block grants. Read about your symptoms and understand this is a disease and its not your fault. Australia, New Zealand, and Malaysia are good resources for new information as their biggest problem is Meth ad often implement new treatments before the United States.

Go to Meetings

Due to Narcotics Anonymous approach to addiction of attraction over promotion I will not say much other then statistically for long term recovery this is your best option. The only requirement is a DESIRE to stop using……

Supportive Research Articles and Studies

I

TREATMENT APPROACHES FOR USERS OF **METHAMPHETAMINE**

a practical guide for frontline workers

TREATMENT APPROACHES FOR USERS OF **METHAMPHETAMINE**

a practical guide for frontline workers

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Introduction

Stimulants such as amphetamine have been used by some people in Australia for many years. However, a more potent form, methamphetamine, has come to dominate the illicit stimulant market over the past decade. Because of its potency, many users have experienced a range of significant physical and psychological health problems.

Alcohol and other drug (AOD) workers from a variety of service settings are now frequently required to respond to methamphetamine users who are experiencing the harmful effects of methamphetamine, going through withdrawal or seeking methamphetamine-specific treatment.

Clinical treatment guidelines that provide a step-by-step guide to structured counselling are available for trained AOD workers such as *A Brief Cognitive Behavioural Intervention for Regular Amphetamine Users* (Baker et al 2003) and *Clinical Treatment Guidelines for Alcohol and Drug Clinicians. No 14: Methamphetamine Dependence and Treatment* (Lee et al, 2007). However, the Australian Government Department of Health and Ageing recognises that clear and up-to-date information is required by all AOD workers, not just those with a clinical or professional background; hence, this publication has been developed to bridge an identified gap in available resources.

The guide is based on recent research, national and international guidelines, and expert opinion. Because a comprehensive review of the research literature was undertaken for the Commonwealth Monograph *Models of Intervention and Care for Psychostimulant Users* (Baker et al 2004) and published in 2004, the literature from 2003 to the present was reviewed for this guide. Databases including PubMed and PsychInfo were used to find studies on relevant topics. Guidelines from Australia and overseas were also consulted and form the basis for a range of topics.

The signs of methamphetamine overdose are now well recognised and frontline workers are advised to familiarise themselves with the emergency management techniques detailed in Chapter 4 *Recognising and managing overdose*.

Best practice in methamphetamine treatment involves a clear, mutually acceptable treatment plan that is designed to meet the needs of the individual. Early engagement, good communication and the development of a strong helping relationship between the worker and service user or client are important to attract methamphetamine users into treatment and to keep them engaged.

Numerous high-quality studies have suggested that psychosocial treatments, especially cognitive behaviour therapy (CBT), should be a standard intervention in methamphetamine treatment. CBT also assists with mental health problems, such as depression and anxiety, which are common among methamphetamine users.

Dependent psychostimulant users experience withdrawal symptoms when they stop using the drug. Although we do not know a lot specifically about methamphetamine withdrawal yet, evidence suggests that, for mild cases of withdrawal, medication is not usually required and most symptoms resolve within two weeks. In contrast, users with more severe dependence might go on to have a longer and more intense withdrawal, and need targeted ongoing support.

In circumstances where a methamphetamine user does not wish to stop using the drug, harm reduction interventions are recommended and a range of suggestions are offered in the guide.

Finally, where research evidence is lacking regarding issues such as methamphetamine use among young people and those from culturally and linguistically diverse backgrounds, the Indigenous community and pregnant women, advice based on good practice and expert opinion is included to provide a starting point to guide workers' responses.

Summary of important points from each chapter

Chapter 1: About methamphetamine (p.13)

- Methamphetamine is a strong **stimulant** that comes in various forms such as 'ice' (a potent, crystal form that can be smoked or injected), base (an oily powder or paste that can be injected), powder ('speed' or 'louie' that can be injected or 'snorted' into the nasal passage) and tablets that are usually swallowed.
- All methamphetamine forms quickly raise and sustain levels of the brain's chemical messengers (**neurotransmitters**), particularly **dopamine**, which is responsible for memory, attention, purposeful behaviour and pleasurable feelings.
- Over time, neurotransmitters become depleted, leading to poor concentration, low mood, lethargy and fatigue, sleep disturbances and lack of motivation.

Chapter 2: Effects, risks and harms, and how these can be reduced (p.19)

- Although there is variation between individuals, **short-term effects** include euphoria, alertness, increased confidence and wakefulness. Higher doses can cause agitation, sweating, tremors, irritability, teeth grinding, anxiety or panic, paranoia and hallucinations (seeing or hearing things that others cannot).
- **Longer-term effects** of regular use can include weight loss; dehydration; poor appetite or malnutrition; kidney problems; mood swings including depression; anxiety; paranoia; chronic sleep disturbance; changes in brain structure and function leading to memory, thinking, and emotional disturbances; disrupted decision making ability; grossly impaired contact with reality (psychosis); and dependence on methamphetamine.
- Due to the high potency of crystal methamphetamine, smoking and injecting ice can rapidly lead to **dependence** in some users.

- **Risks of use** include vein infections from injecting; blood-borne virus (BBV) transmission; heart infection (endocarditis); heart attack; brain haemorrhage; lung and skin infections; poor oral health including tooth decay and gum disease; poor nutrition; psychosis and other mental health problems; and social, occupational and legal problems.
- **Harm reduction approaches** include good diet; regular fluids; adequate rest; regular breaks from using; good oral hygiene (brush and floss regularly); contact with supportive and stable friends and family; education about effects, signs of overdose and psychosis; and advice to seek professional help if psychotic symptoms emerge.
- **Pregnant** methamphetamine users should receive regular antenatal care to reduce risks and to improve outcomes for both mother and baby. Even if psychostimulants have been used in the earlier stages of pregnancy, there are possible benefits of reducing or ceasing use in the later stages. Pregnant users should avoid use of other drugs, such as alcohol and tobacco.

Chapter 3: Recognising and managing intoxication (p.25)

- **Signs of methamphetamine intoxication** can include rapid or difficult-to-interrupt speech; restlessness or agitation; jaw clenching and teeth grinding; sweatiness; large pupils; irritability.
- **An appropriate response** involves sound communication skills; prompt response to a service user's needs; avoidance of lengthy questioning; provision of written materials for later reference; opportunistic brief interventions if possible; and the maintenance of a calm, safe, supportive and helpful environment.
- Do not attempt to interview or counsel an intoxicated client, offer another appointment if required.

Chapter 4: Recognising and managing overdose (p.27)

- Methamphetamine **overdose** (toxicity) is a medical emergency.
- Signs of **toxicity** include hot, flushed or very sweaty skin, which may indicate high fever or overheating; severe headache; chest pain; changes in consciousness; muscle tremor, spasm or fierce jerky movements; severe agitation or panic; difficulty breathing; changes in mental state (eg confusion, disorientation); seizures (fits); and symptoms of psychosis can also occur.
- First aid includes **calling an ambulance immediately** even if unsure of cause; providing a non-stimulating and safe environment; making sure the person can breathe; cooling the body (loosen restrictive clothing, use ice

packs); removal of dangerous objects if the person has a seizure; continual reassurance and waiting with the person until the ambulance arrives.

Chapter 5: Recognising and responding to a person with mental health problems (p.29)

- Methamphetamine users can experience **mental health problems** such as depression, anxiety or psychosis. Symptoms often resolve when the user cuts down or stops using, but some people experience longer-lasting symptoms.
- **Symptoms of psychosis** may be low-grade or 'subacute' and can include: deterioration in general functioning in day-to-day life; expression of unusual thoughts or ideas, strange, inappropriate or out-of-character conversational style; fear or paranoia; a sense of self, others or the world being different or changed in some way; suspiciousness or constant checking for threats in an exaggerated way; over-valued ideas (ordinary events have special significance or are more meaningful than usual); illusions (misinterpretation of surroundings); and erratic behaviour.
- Psychosis in its acute form describes a disorder in which a person's contact with reality is grossly impaired. Symptoms include hallucinations (hearing, seeing or feeling things that other people cannot); delusions (fixed, false beliefs); disordered thought processes; disturbance in mood; and strange, disorganised or bizarre behaviour.
- Methamphetamine can cause a psychotic episode in healthy people with no previous history of mental health problems. It can also trigger a mental health problem such as schizophrenia in vulnerable people, which will endure even after they stop using the drug (for a diagnosis of schizophrenia at least one obvious psychotic symptom must persist for longer than a month in the absence of drug use or withdrawal).
- Psychosis is more likely among dependent methamphetamine users, injectors, and those with other health problems.
- Many people will spontaneously recover from psychosis within hours, as the effects of the drug wear off, while some will go on to experience symptoms for some time.
- **Immediate management of psychosis** includes reducing risk to the person, other workers and bystanders; a calming environment; effective communication (eg never argue, calm voice, repetition of key messages); calling an ambulance to facilitate an emergency assessment if the person remains acutely disturbed; or calling police if risk of harm to self or others is high.

- **Longer-term management of psychosis** includes interventions aimed at discontinued use; education regarding sensitivity to future psychotic episodes; lifestyle management; and harm reduction strategies for those who do not want to stop using (eg regular breaks from using; advice not to use more than small amounts; avoidance of use of multiple drugs; and early intervention should symptoms recur).
- **Depression** commonly occurs among methamphetamine users. Symptoms of depression (eg withdrawal from social contact; negative thoughts; feelings of sadness, guilt, pessimism; changes in appetite, libido and energy) may persist for weeks, months or in some cases even several years after stopping methamphetamine use.
- Workers and clients should regularly review symptoms of depression and seek specialist help if symptoms worsen, especially if suicidal thoughts occur.
- A depressed person might be at high risk for suicide if he or she has tried before; has a clear and lethal plan with the means to carry it out; has a lot of stressors; feels hopeless; has psychotic symptoms; continues to use alcohol and other drugs; or has few or no social supports.
- Clients considered to be at high risk should have an urgent and thorough specialist assessment by mental health services. Workers should keep the contact number for emergency mental health services on hand and refer appropriately.
- **Anxiety** can occur in many forms and usually involves excessive worry. Other features of anxiety can include agitation; racing heart; sweatiness; difficulty breathing; tightness in the chest or chest pain; fear or panic; and sleep disturbance.
- Anxiety symptoms often subside when the drug is no longer used, but if symptoms persist after stopping, a mental health specialist should assess the client. Cognitive behaviour therapy is an effective intervention for anxiety disorders.
- Anxious clients should be provided with a low-stimulus environment and encouraged to take slow, deep, calming breaths. Other relaxation strategies include tensing and relaxing all the large muscle groups in the body; and actively imagining a peaceful, safe place of the client's own choosing.
- Workers should keep the contact numbers for both emergency and non-emergency mental health services on hand at all times and familiarise themselves with procedures for appropriate referral or consultation.

Chapter 6: Helping a person get through withdrawal (p.43)

- Many **recreational users** will experience a 'crash' period after they stop using, which lasts a few days. During this time, they often sleep and eat a lot, can become irritable, and might feel 'flat', tired and lethargic or generally out of sorts. They usually do not require specialist assistance during this 'coming down' period.
- Some **dependent users**, however, will experience full-scale methamphetamine withdrawal, which often lasts for about a week or two. For some people, certain symptoms, such as depression, can linger for several weeks, months or even longer.
- During **withdrawal**, a person can feel depressed; irritable or anxious; be agitated; have difficulty sleeping; be unable to experience pleasure; have poor concentration and memory; have aches and pains; and strong cravings to use methamphetamine.
- Support includes written materials and education about typical length of withdrawal and common symptoms; the need for self-monitoring symptoms of depression and intervention if severe; management of cravings; relapse prevention; and relevant referral to a general practitioner for medical support if insomnia, symptoms of anxiety or depression linger or place the client at risk of relapse.

Chapter 7: Use of other drugs and possible effects of mixing drugs (p.47)

- Use of **multiple drugs** with methamphetamine, particularly **alcohol**, **nicotine**, **cannabis**, **heroin** and **benzodiazepines**, is common.
- Dangerous effects can result when medications for depression (antidepressants) are taken within two weeks of using methamphetamine and can include overheating, high blood pressure, and seizures (serotonin toxicity).
- **Heroin** used in conjunction with methamphetamine increases risk of heroin overdose.
- Methamphetamine can stop people from feeling drunk after drinking alcohol, even when blood alcohol levels are high. Therefore, the risk of accident and injury is increased, as is the potential for driving while intoxicated. Clients with problems related to the use of alcohol need targeted interventions.

- Methamphetamine can also stop people from feeling the full effects of benzodiazepines, leading to increased risk of accident and injury. There is also the potential to take large quantities of benzodiazepine, which increases risk of dependence and subsequent withdrawal. Some people can experience withdrawal symptoms if benzodiazepines are stopped abruptly after just one month. Signs of benzodiazepine withdrawal include sensitivity to loud noises/light/touch; feelings of unreality; numbness; anxiety, fear of open spaces (agoraphobia) and panic states; metallic taste in the mouth; pain, stiffness and muscular spasms resulting in headaches and muscle twitching; and seizures.
- Methamphetamine reduces the effectiveness of **antipsychotic medication** and increases risk of seizures.
- Users should be informed of the potential for harmful effects of mixing methamphetamine and medications and advised to **seek advice from the prescribing doctor**.

Chapter 8: Overview of the range of treatment options (p.53)

- Approaches to methamphetamine users should be individually tailored and match each client's goals for treatment.
- **Cognitive behaviour therapy** has been evaluated most extensively and is effective for a range of problems related to methamphetamine use, including mental health problems such as depression and anxiety. Medicare pays for up to 12 sessions of counselling by a registered psychologist if a general practitioner refers clients.
- Other approaches include brief interventions; counselling (eg narrative therapy, solution-focused therapy); residential rehabilitation; self-help groups; and behavioural therapy.
- Assessments should be offered in the context of a safe, reassuring, supportive, nonjudgemental environment to enhance a client's engagement with the service. In the early stages, this may be more important than the specific drug treatment.
- No medications have yet proven to be more effective than others in treatment (eg for withdrawal or to prevent relapse). However, research is continuing into several medications including dexamphetamine and modafinil. Following a specialist assessment, the appropriate prescription of medications to treat mental health and medical problems is strongly recommended.

- **Young people** can benefit from a thorough assessment of factors such as leisure and social functioning; family relationships; peer interactions; hobbies; and educational history. Intensity of treatment should be matched to the severity of problematic methamphetamine use. Treatment approaches should be youth friendly and include easy access, drop-in capability, follow-up, collaboration between service providers and family therapy.
- Workers should be sensitive to the cultural and social needs of **Indigenous** clients and those from **culturally and linguistically diverse (CALD)** backgrounds. Considerations include the provision of culturally appropriate information including media other than print (eg art or video); role of family in the client's life; need for translation services; outreach service and case management; and culturally appropriate harm reduction messages.
- Services should respond promptly to all clients' requests for help; provide support and assistance with immediate concerns before offering targeted interventions for methamphetamine use; have information readily available; attempt to address a range of user's needs; and actively assist clients to access other services as required.

Chapter 9: Assisting families, carers and significant others (p.71)

- Disruption to **family and other relationships** is common in the context of methamphetamine use.
- Families should be encouraged to access support for their own needs (eg mutual support groups; telephone support and advice; educational materials) and ensure that they continue to live their own lives while they continue to care for their family member.
- Families should be provided with information on how methamphetamine works including the range of possible effects. This should include information about the 'crash' period and withdrawal symptoms, how regular methamphetamine use can adversely affect a person's mood, concentration, and decision-making abilities, and the risks of dependence and psychosis.
- Families require assistance with developing an emergency plan should serious consequences such as hostility or violence, or psychosis arise (see Appendix 2, *Example family emergency plan*).
- Methamphetamine use can sometimes affect the ability to parent, so others might take on the role of caring for a client's children until he or she is better equipped to do so. In this case carers should be encouraged to access ongoing support and practical assistance (eg financial support).

- **Young carers** should also be encouraged to pay attention to their own lives and pursue interests appropriate to their age. They should be encouraged to seek support from appropriate sources (eg school counsellor, teacher, trusted relative, kids help line, or dedicated websites such as http://www.youngcarers.net.au), and to develop an emergency plan (see Appendix 3, *Example young carer's emergency plan*).

Chapter 10: Legal issues (p.79)

- **Interventions** tend to be as effective for people who are pressured to enter treatment (coerced clients) as for those who seek help voluntarily.
- **Coercion** can be formal (eg court ordered) or informal (pressure from a spouse or family).
- Clients who have been formally coerced into treatment should be informed of which agencies and under what circumstances workers are legally obliged to disclose information regarding the client's progress without his or her consent.
- Informally coerced clients should give consent before any information about their progress can be shared with their spouse, family member or significant other.
- **Mandatory reporting** describes legislation that requires some workers to report all cases of suspected or confirmed child abuse and neglect. As legislation varies across each state and territory, workers have a duty to be familiar with mandatory reporting requirements in their own state or territory.
- Although there is a perception that all methamphetamine users are violent, this is not the case. Rates of violent crime, although higher than the general population, tend to be restricted to methamphetamine-dependent, multiple-drugs users with a history of violence. Violence, when it does occur, usually happens when people are paranoid or psychotic. Therefore, hostility and violence is often time-limited, and tends to occur only when symptoms are acute.

Chapter 11: Making links and creating partnerships (p.83)

- **Service partnerships** can help facilitate timely, appropriate and targeted responses to a client's needs, minimise access barriers for clients, and ultimately improve client outcomes.
- Services should identify appropriate or helpful agencies for potential partnerships; decide on the level of cooperation or collaboration that would be useful; initiate contact; agree on a desired outcome for cooperation; ensure regular liaison, prompt responses, support, and ongoing education for partner agencies; and evaluate the effectiveness of partnerships.
- Staff members should learn and use **appropriate terminology** when referring a client to other agencies, particularly mental health services and general practitioners.
- **Referral** can be improved by ensuring that workers address the client's pressing needs first, before suggesting referral to another agency for assistance with less important matters; enhancing awareness of other useful agencies or services including location, hours of opening, cost, who is eligible for assistance, and waiting times for service; understanding the needs of the client (eg financial resources; access to transport; requirement for child care; cultural and social issues; level of ability to advocate for self; literacy level; mental health concerns) prior to making a referral; and matching referral to a client's need.

1
About methamphetamine

What is methamphetamine?

Methamphetamine is a synthetic substance that can come in various forms:

- crystalline ('ice', 'crystal', 'crystal meth', 'shabu', 'glass')
- oily powder or paste ('base')
- coarse or fine powder ('speed', 'louie')
- tablet ('pills')
- oil (base) is the least commonly available form, but it is the purest form that is converted by manufacturers into the other forms; base is stronger than powder forms and nonadulterated crystal is estimated to be about 80% pure.

The chemical structure is similar to amphetamine, but methamphetamine tends to be more potent than amphetamine sulphate and amphetamine hydrochloride (also called 'speed'), which were typically used before the mid-1990s. The stimulant effects of methamphetamine can last from 7 to 24 hours or even longer, depending on the form used (for photographs of methamphetamine forms see the fact sheets at http://ndarc.med.unsw.edu.au).

Methamphetamine can also be mixed with a range of other substances or drugs. For example, methamphetamine is sometimes mixed with ketamine, a powerful anaesthetic, to form a tablet that is then commonly sold to users as *ecstasy* (for information on ecstasy, see http://www.druginfo.adf.org.au/article.asp?ContentID = ecstasy).

How many people use methamphetamine?

Every three years, the Australian Government undertakes a study in which a representative sample of Australians, aged 14 years and over, is asked about

their use of drugs. This survey is known as the National Drug Strategy Household Survey. In 2007:

- meth/amphetamine had been used at some time in the life of 6.3% of those surveyed
- the highest proportion of recent meth/amphetamine users were those in the 20–29-year age group (9% males and 4.8% females)
- two-thirds of injecting drug users identified meth/amphetamine as the drug injected most recently, compared with heroin at 39.7%.

How and why people use methamphetamine

People use methamphetamine for different reasons and in a variety of patterns:

- Experimental — many people, often adolescents and young people, try a range of drugs once or twice out of curiosity.
- Instrumental — some people use methamphetamine for specific purposes, for example, to stay awake (eg long-distance truck drivers), improve concentration (eg students), reduce weight and enhance endurance (eg for sporting events), or boost energy for a range of other activities.
- Recreational — some people use occasionally, for enjoyment or socialising, at private parties, clubs or dance parties.
- Binge — others use moderate to high doses in an on–off pattern.
- Regular — some people use weekly, several times weekly or daily. Regular users are more likely to be dependent on methamphetamine and have problems with their mental health.

The way that people take methamphetamine generally depends on the form used:

- Powder is often 'snorted' into the nasal passage.
- Ice is often smoked by heating the crystal in a pipe until it is vaporised or by mixing it with cannabis and smoking it ('snow cone').
- Ice and base can also be injected or swallowed (known as 'bombing').
- Smoking methamphetamine, although considered less harmful than injecting by some users, has high potential to lead to dependence due to the rapid onset of euphoria (a strong feeling of wellbeing or elation) and subsequent intense cravings for more of the drug. It is also difficult for smokers to know how much they have used, which can lead to toxic (poisonous) effects.
- Bombing and snorting are common among experimental and recreational users; injecting is typically associated with regular users, and both recreational and regular users smoke methamphetamine.

- Methamphetamine powder is typically purchased by gram or half-gram weights, whereas ice and base are usually bought in a much smaller amount, known as a 'point' or one-tenth of a gram, because of their high potency.

People rarely use methamphetamine exclusively, and the use of multiple drugs, known as polydrug use, is common (see Chapter 7, *Use of other drugs and possible effects of mixing drugs*).

How does methamphetamine work?

The way methamphetamine works is complex, but it is extremely important for workers to understand how this drug works in the body so they can help inform their clients. Understanding the mechanism of methamphetamine's actions, the short- and long-term effects of methamphetamine use, and the impact on a person's mental health helps the worker understand the user's behaviour and treatment options. The end of this section contains a suggested plain language explanation that can be used by workers to help clients better understand the effects of methamphetamine.

Information for workers

Methamphetamine disrupts the brain's chemical messengers known as 'neurotransmitters'. The main neurotransmitters involved are *dopamine, noradrenaline* and *serotonin,* which have a broad range of important functions.

Dopamine controls movement, attention and memory, and purposeful behaviour. It is the main neurotransmitter involved in feelings of pleasure and euphoria when a person engages in activities that are essential for human survival, such as eating, drinking, and sexual activity. Dopamine encourages these behaviours by making people feel good so they are motivated to repeat them. This system is referred to as the 'reward pathway' and, because dopamine is also linked to cravings to use all drugs, it is thought to be involved in the development and maintenance of drug dependence in general.

Noradrenaline is involved primarily in preparing individuals to either run away from, or stand and fight against, perceived threats ('fight or flight' response): it stimulates the central nervous system, and is involved in heart function and blood circulation, concentration, attention, learning and memory.

Serotonin is involved in a variety of important activities including control of mood; appetite; sleep; thinking and perception; physical movement; regulation of temperature, blood pressure and pain; and sexual behaviour.

Short-term use

Methamphetamine quickly and substantially raises the levels of these neurotransmitters and stops them from being cleared (known as 're-uptake'), so their levels remain high for a much longer time than usual. (Selective serotonin reuptake inhibitor [SSRI] antidepressants also work in this way, but this is beneficial in depressed people who have low levels of these transmitters without treatment.) Methamphetamine causes the brain cells to be awash with dopamine, which markedly accelerates the normal bodily processes. A person will be alert and energetic, and have an intense feeling of wellbeing (euphoria). The euphoria is usually much more intense and lasts longer than that felt from natural survival behaviours. For example, in animal studies, dopamine level increases by around 50% after eating, but increases tenfold after administration of methamphetamine (see Chapter 2, *Effects, risks and harms, and how these can be reduced*).

After a while, stores of these neurotransmitters peter out, and the levels drop from too high to too low, like overdrawing a savings account. When the level is low, a person can experience a range of symptoms of varying intensity that are mostly the opposite to those of intoxication: low mood, lethargy and fatigue, poor concentration, disturbed sleep, increased appetite, and lack of motivation for daily tasks. It takes some time for the neurotransmitters to be replenished (adequate diet, rest and avoidance of methamphetamine are critical for this), during which time the person might continue to feel out of sorts and have difficulty taking pleasure in normal activities. Recovery or 'coming down' from short-term or binge exposure might take the person a couple of days to a week (see Chapter 6, *Helping a person get through withdrawal*).

Long-term use

Both animal and human studies have shown that long-term exposure to heavy methamphetamine use leads to both short-term neurotransmitter depletion and changes in brain structure and function. To reduce overexposure to neurotransmitters, particularly dopamine, the body responds by reducing both the number of receptors (receivers) and transporters (carriers) of these neurotransmitters in certain parts of the brain. In addition, brain cells themselves can be killed (neurotoxicity) as they struggle to break down excess dopamine. The result is chronic dopamine *underactivity*, resulting in damage to memory, concentration, decision-making, impulse control, and emotional balance.

The recovery period after long-term use, during which complete avoidance of methamphetamine should be maintained, can take many months or even years. Some researchers believe that certain individuals, particularly long-term regular users who began using methamphetamine at an early age, may never recover completely (see Chapter 2, *Effects, risks and harms, and how these can be reduced*).

Information for clients

The following explanation could be helpful for some clients. Workers could also use visual images or drawings to aid understanding:

> Methamphetamine causes the brain to release a huge amount of certain chemical messengers, which, as you probably know, make people feel alert, confident, social, and generally great. Some of these messengers help us to respond to threats by preparing us to either fight or run away, so they increase energy, keep us awake, stop hunger and raise blood pressure and heart rate.
>
> The problem is that there are only so many of these messengers stored at any one time. Think of a glass full of 'happy' messengers, so when people have been using methamphetamine for a while, the glass empties and no matter how much methamphetamine they use, they just can't get the 'rush' they want and will still feel awful. There are just too few messengers left to tell the brain to feel good. It's like overdrawing a bank account — no matter how many times you go back to the bank, the balance is still zero until a deposit is made.
>
> It takes rest, a good diet, and most of all TIME for the glass to become full again. During this period, people can feel flat, moody, irritable, forgetful, and restless, but exhausted, which is opposite to the feelings people have while using. This is when people often get strong cravings to use methamphetamine because these cravings are caused by the same brain chemical messengers, which are being produced, but in only small amounts.
>
> Researchers think that, after using methamphetamine regularly over several years, some people experience a long-term or chronic lack of these 'happy' messengers, which can cause people to feel moody, have trouble concentrating and making decisions, and either lack motivation to do usual things or behave in reckless ways. This can sometimes last for months or even a year or two.
>
> The main issues in treatment are to make sure that your mood doesn't get too low; improve your general health by eating a good diet and getting plenty of rest; manage cravings; and take things day by day so you don't get frustrated with your progress and go back to using.

References Chapter 1: About methamphetamine

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2
Effects, risks and harms, and how these can be reduced

What are the short-term effects?

The effects of methamphetamine depend upon a range of factors including the quality and purity of the drug; amount used; how it is used; the person's tolerance to methamphetamine (eg new or regular user); where it is used (eg crowded, hot dance party or person's home); and the person's general physical and mental health. Although there is individual variation in the effects of the drug, the following points serve as a guide:

During intoxication

During *intoxication*, the person usually feels a sense of wellbeing or euphoria and is alert, energetic, wakeful, extremely confident — sometimes invincible— with a sense of heightened awareness and increased concentration. Libido (sex drive) and blood pressure often increase. The person may be talkative and fidgety or restless, and will have large (dilated) pupils. Appetite is reduced. Wakefulness varies, but might continue for 12 hours or more.

At higher doses

At *higher doses*, the person might experience tremors, anxiety, sweating, palpitations (racing heart), dizziness, tension, irritability, confusion, teeth grinding, jaw clenching, increased respirations (breathing); auditory (hearing), visual or tactile (touch) illusions; paranoia and panic state; loss of behavioural control; or aggression.

In overdose

In *overdose* (toxicity), the person can experience intense paranoia involving hallucinations (hearing or seeing things that are not there) and delusions (eg having a fixed false belief often that people or things mean the person harm). The person can also experience chest pain and shortness of breath; severe headache; tremors; hot and cold flushes; dangerously increased body temperature; muscle spasms; brain haemorrhage; heart attack; or seizures (fits) (see Chapter 4: *Recognising and managing overdose*).

What are the long-term effects?

Long-term use of methamphetamine can result in a number of physical and psychological effects, which are often related to poor diet, lack of sleep, dehydration and ongoing (chronic) neurotransmitter disruption including:

- weight loss and dehydration relating to poor nutrition or malnutrition; irregular or absent menstrual periods; renal (kidney) problems caused by the lack of adequate fluid intake; chronic sleeping problems; and probable methamphetamine dependence
- extreme mood swings including depression and possibly suicidal feelings; anxiety; paranoia; and psychotic symptoms including hallucinations and delusions (see Chapter 5: *Identifying and responding to a person with mental health problems*)
- cognitive (thinking) changes including memory loss, difficulty concentrating, and impaired decision-making abilities.

What are the other risks and harms?

Users of methamphetamine are at risk for a range of other potential harms including:

- blood-borne viruses (BBV), including hepatitis B and C and human immunodeficiency virus (HIV) from sharing injection equipment
- infections and damage to veins (cellulitis)
- heart problems such as irregular heart beat, weakened heart muscle (cardiomyopathy), bacterial infections of the lining of the heart (endocarditis), and heart attack (myocardial infarction)
- burst blood vessels in the brain (stroke, ruptured aneurysm, brain haemorrhage)
- shortness of breath and dizziness in smokers of ice
- sexually transmitted diseases including HIV and syphilis linked to sexual risk taking
- poor oral health such as gum inflammation (gingivitis) and cavities caused by methamphetamine-induced dry mouth, and damaged teeth due to grinding and jaw clenching
- feelings that 'bugs' are crawling under the skin (tactile hallucinations)
- compulsive skin picking and scratching, particularly on the face and arms, which can increase vulnerability to skin and other infections
- family and other relationship breakdown; financial problems; loss of employment; and legal problems related to drug driving, dealing, or engaging in other crimes to support continued use.

How can the risks and harms be reduced?

A harm reduction approach should be taken with all methamphetamine users who intend to continue to use and will not consider stopping.

Users come to services with a wealth of knowledge about drug use already, so it is important for workers to ask what clients already know and what they would like to know so harm reduction advice can be tailored, appropriate and engaging.

As well as the usual safer injecting and safer sexual practices advice, which is freely available in a wide range of resources, some harm reduction strategies specifically for users of methamphetamine have been recommended (see http://www.aivl.org.au or http://www.hepatitisc.org.au) or contact the local alcohol and drug information service.

Workers should encourage clients to do the following.

Eat and drink enough

- Drink plenty of water — keep a water bottle handy and take frequent sips because people tend to forget to drink when they are intoxicated and on the go, and can easily become dehydrated.
- Eat a balanced diet including dairy products, meat and fish (or non-animal protein for vegetarians), fruit, vegetables, rice, grains, nuts, etc. Workers can help by checking a client's weight regularly.
- Drink milk, high protein drinks, shakes or fruit smoothies if solid food cannot be tolerated. (*You wouldn't run a long distance marathon without eating or drinking so you need to put some fuel into your body.*)

Rest sufficiently

- Get adequate rest. (*Going more than two nights without sleep isn't good for anyone.*) Encourage regular users to have regular non-using days each week, or plan a 'crash' period when they can rest and sleep undisturbed for several days to 'come down'.
- Get into regular patterns of eating, drinking and resting as detailed above. Even if users do not feel hungry, a little food and good hydration helps.

Understand the actions and effects of methamphetamine

- Understand how methamphetamine works (see Chapter 1 *About methamphetamine*).
- Be clear about individual signs and symptoms of psychosis. If psychotic symptoms are experienced, take a total break from using methamphetamine and seek professional help from the person's GP, local emergency department, or local mental health service (see Chapter 5, Recognising and responding to a

person with mental health problems).

- Call on friends or family who are stable supports in the person's life if he or she is feeling scared, paranoid or panicky. Support people can often help the client calm down or can call for specialist help if needed. Users could make an emergency plan and have names and numbers of support people handy.
- Be clear about signs and symptoms and overdose including advice to call an ambulance immediately if overdose occurs (see Chapter 4, *Recognising and managing overdose*).

Attend to other health and lifestyle issues

- Brush and floss teeth regularly, and chew sugar-free gum to increase saliva and to take some pressure off the enamel if teeth grinding is a problem. Dental health can suffer due to a lack of bacteria-fighting saliva in the mouth.
- Plan for the week ahead and make sure that the person does not use (or be in the middle of 'coming down') just before an important event or commitment (workers might need to assist clients to brainstorm alternatives to using). This will help to keep life a little more on track.
- Consider if the person is doing things that they would not normally do to buy methamphetamines. Sometimes a person does not realise that his or her life is out of control, and a client's own moral compass is a good indicator.
- Avoid discussing sensitive topics or making important decisions if partners are coming down together. Social or romantic relationships can suffer when people are feeling irritable, so encourage partners to be patient with each other.
- Avoid driving when intoxicated or 'coming down', particularly if alcohol has also been consumed.

What about pregnancy?

Workers in the drug and alcohol field are sometimes asked for advice about drug use during pregnancy. There is only limited evidence about the specific effects of methamphetamine on the developing foetus in humans, and most evidence comes from animal studies or is derived from studies on cocaine or 'crack' use.

The most important thing for a pregnant woman is to have regular, supportive antenatal care, which improves outcomes for both the mother and baby. The specialists in the antenatal team can assess each woman and offer individual advice and guidance throughout the pregnancy. It is not uncommon for women to be reluctant to disclose drug use, as they often fear criticism, or dread having the baby removed from their care. However, antenatal teams focus on the best interests of the mother and child, and play a crucial role in improving the likelihood of a healthy pregnancy.

Workers can assist a pregnant user by establishing strong networks and collaborating with specialist antenatal teams who see mothers at risk for complications. Antenatal teams can be contacted through the local hospital. (See Chapter 11, *Making links and creating partnerships* for advice about networking).

Workers could encourage pregnant clients to talk to other mothers who have had a good or positive experience with a local antenatal team to relieve the client's fears.

If the mother declines antenatal support and workers are concerned about the welfare of the baby or other children in the mother's care, workers should consider the role of child protective services. Workers should refer to the guidelines for mandatory reporting and seek advice from a supervisor if in doubt (see Chapter 10 *Legal issues*).

Concerns about foetal development in babies of methamphetamine users

Based on limited research, some of the concerns for pregnant methamphetamine users include the risk:

- that methamphetamine use will affect organ development during the early weeks of the pregnancy, which can cause for example, cleft pallet or heart defects
- that the foetus will not receive the oxygen and nutrients essential for normal growth and development, including brain development (eg risk of premature birth, low birth weight or subtle brain changes)
- of foetal toxicity in the third trimester (weeks 24 to birth) because it takes the developing foetus nearly twice as long as the mother to clear drugs from its system, placing the baby at significant risk for methamphetamine withdrawal after birth
- of other health-related issues linked to the mother's lifestyle such as inadequate rest, nutrition, and hydration; cigarette smoking and use of other drugs including alcohol (which puts the baby at risk for foetal alcohol syndrome[1]); increased maternal blood pressure; exposure to impurities in street methamphetamine; and being a victim of violence.

Concerns for breastfed babies of users

Methamphetamine use reduces quantity of breast milk and methamphetamine can be released into breast milk (methamphetamine has been found in the urine of babies of users). Infants breastfed by methamphetamine-using mothers may experience a range of drug-induced behavioural problems such as irritability,

1 Foetal alcohol syndrome can result in low birthweight, smaller than normal head circumference, small eyes, flattened face and heart defects. Later in life, affected children might experience low IQ, developmental delays, behavioural problems, learning difficulties and memory problems.

poor sleeping patterns, agitation and crying. New mothers who continue to use methamphetamine can often still breastfeed their infants; however, antenatal team specialists are best placed to advise mothers about the best ways to limit risks to the baby.

Advice for pregnant women

Pregnant women and new mothers who use methamphetamine should be encouraged to seek regular, effective health care during and after the pregnancy to improve maternal nutrition, reduce psychological distress and improve outcomes for newborns.

Pregnancy can be a strong motivator for change in some women, and workers can skilfully employ motivational approaches during this time.

Pregnant users should be advised to avoid other substance use; especially nicotine, cannabis and alcohol, as abstaining from these substances can also improve neonatal and early childhood outcomes.

Even if methamphetamine has been used in the earlier stages of pregnancy, there are possible benefits for reducing or ceasing use in the later stages, which should be discussed with specialists in the antenatal team.

References Chapter 2: Effects, risks and harms and how these can be reduced

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3
Recognising and managing intoxication

Intoxication: what to look for

Signs of methamphetamine intoxication vary according to the amount of methamphetamine (and other drugs) taken and can include the following:

- rapid or pressured speech (fast, loud and difficult-to-interrupt speech), or jumping from one topic to another
- restlessness, agitation, pacing
- repetitive movements
- impulsivity or recklessness
- clenched jaw, teeth grinding (bruxism)
- sweatiness
- suspiciousness or paranoia
- large (dilated) pupils
- anger, irritability, hostility, particularly if it is out of character

Responding to an intoxicated person

The aims of responding to a person who is intoxicated are to maintain a calm environment to reduce the chance that the person will become angry or hostile and to promote a positive, helpful interaction. **Remember that an intoxicated person has impaired judgment and will probably see the interaction differently to you.**

What you should do

✔ If other people are present, try to steer the intoxicated person to an area that is less stimulating while ensuring that the client and worker both have an easily accessible exit.

- ✔ Maintain a calm, nonjudgmental, respectful approach.
- ✔ Listen, and respond as promptly as possible, to needs or requests. (*I hear what you are saying, so let me see what I can do to help.*)
- ✔ Allow the person more personal space than usual.
- ✔ Use clear communication — short sentences, repetition, and ask for clarification if you are unsure what is said. (*I really want to help, but I'm not sure what you need. Please tell me again.*)
- ✔ Move around with the intoxicated person to continue communication if necessary.
- ✔ Have written information available for the person to take away.
- ✔ Provide opportunistic, relevant, brief interventions if you are able.

What you should not do

- ✖ Do not argue with the person and do not use 'no' messages. If you cannot provide what they are asking for, be clear about what you *can* provide.
- ✖ Do not take the person's behaviour or any criticisms personally.
- ✖ Do not ask a lot of questions — ask only what is necessary to respond to the situation, as the person will have low tolerance for frustration or questioning.
- ✖ Do not undertake a lengthy interview or try to counsel the person — if the person has presented for assessment or counselling, inform him or her that you cannot continue if he or she is intoxicated and agree to make a future appointment.

References Chapter 3: Identifying and managing intoxication

Lee N, Johns L, Jenkinson R, Johnston J, Connolly K, Hall K and Cash R (2007). *Clinical Treatment Guidelines for Alcohol and Drug Clinicians. No 14: Methamphetamine Dependence and Treatment*. Turning Point Alcohol and Drug Centre Inc, Fitzroy.

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4
Recognising and managing overdose

Methamphetamine overdose: what to look for

Methamphetamine overdose (toxicity) is a medical emergency. If untreated, overdose can lead to heart attack, stroke, breakdown of muscle tissue (rhabdomyolysis), kidney failure, and possibly death.

In addition to those listed for intoxication in the previous chapter, signs of toxicity include:

- hot, flushed or very sweaty skin, which may indicate high fever
- severe headache
- chest pain
- unsteady walking (gait)
- muscle rigidity, tremors, spasm, fierce jerking movements of the limbs, seizures
- severe agitation or panic
- difficulty breathing
- altered mental state (eg confusion, disorientation).

Symptoms of psychosis can also occur (see Chapter 5, *Recognising and responding to a person with mental health problems*).

First aid for methamphetamine overdose

✔ **CALL 000 AND REQUEST AN AMBULANCE IMMEDIATELY,** even if you are unsure if methamphetamine is the cause — ambulance officers do not routinely notify police in the event of overdose.

✔ Move the person to a quiet, safe room away from bystanders, noise, excessive light, heat and other stimulation.

- ✔ Remove constrictive or hot clothing; apply icepacks to neck, underarms and groin; or thoroughly wet a towel with cold water and place over the person's body to reduce temperature.
- ✔ If the person is unconsciousness, place him or her on the side with the upper leg bent at the knee to support the body, and tilt the chin upward slightly to maintain a clear airway and avoid any obstruction to breathing.
- ✔ If muscle spasms or seizures occur, remove anything from the immediate environment that might pose risk of injury.
- ✔ Stay with the person until the ambulance arrives and give reassurance that he or she will be attended to as soon as possible.

What not to do

- ✖ Do not attempt to transfer the person to a doctor or hospital yourself or allow others to do so.
- ✖ Do not call a doctor or hospital directly — this simply wastes precious time.
- ✖ Do not leave the person alone.

Recommended service response

It is recommended that each agency or service develop a policy or protocol for identifying and managing overdose in its particular setting. The document should include the signs and management principles listed here, and should incorporate routine staff training and review after an emergency occurs.

References Chapter 4: Recognising and managing overdose

Dean A and Whyte I (2004). Management of acute psychostimulant toxicity. In *Models of Intervention and Care for Psychostimulant Users*, 2nd edition. Baker A, Lee N and Jenner L (eds), Commonwealth of Australia Monograph Series, 85–101. Australian Government Department of Health and Ageing, Canberra.

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5
Recognising and responding to a person with mental health problems

Background

Users of methamphetamine can experience a range of mental health problems (eg depression, anxiety, psychotic symptoms). Some people experience these as a direct result of using the drug, and the problem will improve or resolve rapidly when people stop using or cut down.

Other people might experiences longer lasting psychosis (weeks to months).

Some people might have had a mental health problem before they started to use methamphetamine, for example, schizophrenia, and are likely to experience relapse of psychotic symptoms following methamphetamine use.

Many diagnostic and screening instruments are available to detect a range of mental health disorders (see http://www.adelaide.edu.au/library/guide/med/menthealth/scales.html).

This chapter describes the symptoms of psychosis, depression and anxiety. It includes tips on how to communicate with a person who is experiencing psychosis; how to respond to a client with depression or who is thinking of self-harm; and how and when to refer a client to mental health services.

What is psychosis?

The term psychosis describes a disorder in which a person's contact with reality is grossly impaired. Symptoms of psychosis include:

- Hallucinations — the person experiences sensations that have no basis in reality such as hearing 'voices' (auditory hallucinations), 'feeling' things on the skin or in the body (tactile hallucinations), or seeing things that others cannot (visual hallucinations). Other hallucinations involve taste (gustatory hallucinations) and smell (olfactory hallucinations).

- Delusions — the person holds fixed, false beliefs that do not shift even when faced with logical evidence to the contrary. For example, a person might believe that he or she is being spied upon by a secret agency, or that his or her thoughts are being controlled by external forces. Beliefs that are part of a person's religion or culture are not considered to be delusions unless those beliefs are not upheld by others in the person's same religious or cultural group.
- Thought disorder — a person's thinking becomes confused, concentration becomes difficult, thoughts may speed up or slow down, or the person will jump from one topic to another with no obvious logical connections.
- Disorganised or bizarre behaviour — a person will respond to strange thoughts or unusual sensory experiences by changing their behaviour to adapt to their beliefs or perceptions. To others, their behaviour may seem disorganised or bizarre, but to the person they make sense. For example, those who fear surveillance might pull down blinds; speak in whispers; disconnect the phone; appear generally anxious, jumpy or afraid; and may even keep a weapon for protection.

Mood swings also commonly occur when a person experiences psychosis.

Note: Mood swings, agitation and irritability *without* the presence of hallucinations or delusions does not mean that the person is psychotic. Workers should respond to these people in the usual way, such as providing a calm environment, using de-escalation techniques, and meeting the person's immediate needs.

About methamphetamine psychosis

Stimulants can bring on a psychotic episode in healthy people with no previous history of mental health problems. Many users report experiencing low-grade or 'subacute' psychotic symptoms such as visual illusions, fleeting hallucinations or odd thoughts that come and go. Other users can experience more severe episodes where they hear or see things that are not there, or they become paranoid and believe that other people are going hurt them. The rate of psychosis among regular methamphetamine users interviewed in Sydney recently was 11 *times* that seen in the general population.

Many people will recover spontaneously from psychotic symptoms within hours as the effects of the drug wear off. These people may benefit from a quiet, low-stimulus environment and will not usually need specialist treatment. On the other hand, psychosis can persist for days, weeks, months or longer in some people. In this case, it is likely that those people were already at risk for developing a psychotic disorder and methamphetamine use triggered it. These people need to have specialist mental health treatment, which usually includes medication (antipsychotic drugs).

Although hospital admissions for amphetamine psychosis have increased over the past decade, only a small percentage of people who experience psychosis actually go to hospital for treatment. When they do, it is usually through the emergency department and only when psychosis is severe. As methamphetamine psychosis is more likely in dependent users, multiple presentations to emergency departments are more common among this group.

Some regular users who have been psychotic might become psychotic again when even small quantities of methamphetamine are used. This is known as 'reverse tolerance' (ie even using *smaller* amounts than before can trigger psychosis). These people can also be sensitive to stressors including the use of other drugs or alcohol, which might also trigger a psychotic episode. Some people can experience fleeting psychotic symptoms or 'flashbacks' even after they stop using.

What is schizophrenia?

Psychosis can be fleeting and last for hours, days or a week or two. On the other hand, according to the International Classification of Diseases-10, schizophrenia is a disorder that is characterised by at least one prominent psychotic symptom (or two symptoms if not clear cut) that last for *more than a month,* and is *not related to drug intoxication or withdrawal*. A person with severe, enduring psychosis or schizophrenia also tends to lack insight into his or her symptoms, which means that the person is unable to recognise that hallucinations or delusions may not be real. People with schizophrenia can be stabilised on medication, which means that psychotic symptoms are much less severe, although some symptoms can persist. People who have a mental health problem like schizophrenia are at greater risk of experiencing psychosis than other methamphetamine users.

Methamphetamine psychosis or schizophrenia?

It is extremely difficult to distinguish between methamphetamine psychosis and schizophrenia, and only a psychiatrist can make a diagnosis, so the important thing is to respond appropriately and skilfully to every person who experiences psychotic symptoms (see *Initial response*, page 29). However, those with methamphetamine psychosis:

- have a history of methamphetamine use or have used methamphetamine recently
- have psychotic symptoms that developed during intoxication, withdrawal or shortly after withdrawal
- have psychotic symptoms that subside and resolve within hours as the methamphetamine effects wear off
- do not fit criteria for a diagnosis of schizophrenia.

Impending or 'subacute' psychosis: what to look for

Acute psychotic symptoms are usually easy to identify, although methamphetamine users may present with a range of low-grade psychotic symptoms that are more difficult to pinpoint. The following are signs of low grade or subacute psychosis:

- Suspiciousness, guardedness, hypervigilance[2] — constantly checking for threats in an exaggerated way.
- Overvalued ideas — ordinary events have special significance or are more meaningful than usual or odd.
- Illusions or misinterpreting the environment — eg a shadow might seem like a person walking into a room, or a random sound might seem like a ringing phone or a police siren; or fleeting, low-level hallucinations.
- Erratic behaviour — often related to overvalued or paranoid ideas and might include accusing others of perceived misdeeds, or arguing with bystanders for no apparent reason.

Acute psychosis: what to look for

The following are signs of acute psychosis:

- Delusions — often people feel persecuted; they may believe that others have malicious intentions or that they are under surveillance.
- Hallucinations — often auditory such as 'voices' or sounds like police car sirens, or tactile such as a feeling that 'bugs' are crawling under the skin, but these can also be visual.
- Erratic, uncontrolled or bizarre behaviour often in response to delusions or hallucinations, for example, talking or shouting in response to 'voices'; unnecessary whispering; barricading a room; checking doors; pulling down blinds; making frantic phone calls; keeping a weapon for protection from perceived threats.
- Illogical, disconnected, or incoherent speech
- Extreme or rapid mood swings that are unpredictable, irrational or erratic.

First steps in response

✔ Quickly scan the immediate vicinity and observe location of exits, bystanders, and potentially dangerous objects to judge immediate risks and decide upon the most suitable approach (leave and call for assistance or respond carefully).

2 Due to some users' lifestyle factors, guarded or vigilant behaviour might be appropriate so enquire about this during assessment.

- ✔ If in a public place, service or treatment setting, move bystanders from the immediate environment to avoid risk of injury or escalation of the situation.
- ✔ If in a nontreatment setting or private home, stay close to the exit and remove yourself from any room that might contain dangerous implements or weapons (eg kitchen, workshop).
- ✔ Try to reduce noise, human traffic or other stimulation within the person's immediate environment.
- ✔ Try to determine if the person has recently used methamphetamine either by direct questioning or by asking companions or family.
- ✔ Observe for any physical signs of methamphetamine overdose and respond promptly (see Chapter 4, *Recognising and managing overdose*).
- ✔ If psychosis is severe, arrange transfer to an emergency department for assessment and treatment by **calling an ambulance on 000**. Give them your exact location and name of the nearest cross street; accurately describe what is happening (say exactly what the person is saying and doing); remain calm and ensure everyone's continued safety until the ambulance arrives.

Communicating with a person who is experiencing psychotic symptoms

A skilled response to a person who is experiencing psychosis will assist him or her considerably.

What the communicator should do

- ✔ Choose one worker who will communicate with the person and feels confident to do so — many communicators increase stress, confuse the person, and escalate the situation.
- ✔ The 'communicator' should place other workers on stand-by so a team approach can be undertaken. Have another staff member present to observe or step in *only if required* (the communicator could use a code word to call for assistance from the 'observer'). The observer should attempt to determine if the client has a known history of aggression or violence and, if so, extra care should be taken and the observer should be ready to call for immediate assistance if required.
- ✔ Allow the person as much personal space as possible.
- ✔ The communicator should be aware of his or her body language — arms should be by the sides with palms out and the communicator should make no sudden movements and should approach slowly from the front so the person is not startled.

- ✔ The communicator should mirror body-language signals from the person — sit with a person who is seated, walk with a person who is pacing —to show that the worker understands what the person is going through (empathy) and to ensure that the worker appears neither threatening, by standing over the person, nor vulnerable by being seated while he or she stands.
- ✔ The communicator should monitor and use appropriate eye contact — not too much (appears threatening) or too little (implies indifference or untrustworthiness).
- ✔ Use a consistently even tone of voice, even if the person's communication style becomes hostile or aggressive.
- ✔ Use the person's name if known or the communicator should introduce him- or herself by name.
- ✔ Carefully call the person's attention to their immediate environment. (*You're in the* [service] *and you're completely safe now*).
- ✔ Offer a glass of juice or water, as this can often help calm the person.
- ✔ Use careful, open-ended questioning to determine the cause of the behaviour or the person's immediate needs and communicate your willingness to help. (*I can see that you are really upset; what can I do to help you?*)
- ✔ Listen attentively and respectfully.
- ✔ Ask the person if he or she would like a minute or two to think and respond — consider stepping back to reduce the stimulus while still actively managing the situation. (*I'll give you a minute or two to think, but I'll be right here.*)
- ✔ Always appear confident — this will increase the client's confidence in the communicator's ability to manage the situation, as he or she will probably be feeling scared or anxious too.

What the communicator should not do

- ✖ Do not laugh at or argue with the person's unusual beliefs, even if they are obviously wrong or make no sense at all.
- ✖ Do not agree with or support the unusual beliefs either, as people can usually tell when workers are not being genuine. It is better to simply say:
  - ✔ *I can see that you're scared, how can I help you?*
- ✖ Do not allow the person to block the worker's exit from the room, and do not block theirs.
- ✖ Do not use 'no' language, which may prompt a hostile outburst; rather, use statements like:
  - ✔ *This is what I CAN do for you…* often encourages further communication and has a calming effect.

Note: Is the person threatening harm to him- or herself or others? If so, call the police on 000 immediately and remove all bystanders or other staff members from the location until police arrive. Workers should be aware that psychostimulant use is a risk factor for sudden death of individuals being physically restrained and if restraint is ever necessary, it should be undertaken for the *shortest possible time* (see *Responding to challenging situations: a practical guide for frontline workers*).

Longer-term management

The preferred goal of treatment for a person who has experienced methamphetamine psychosis is to stop using the drug. Motivational approaches that focus on psychosis as a consequence of methamphetamine use could be helpful in achieving this. If psychotic symptoms persist, the person must be treated by mental health specialists, preferably in conjunction with alcohol and other drugs workers, and workers should encourage the person to take psychiatric medications as prescribed (see *Referring to mental health services* later in this chapter).

It is important to encourage the person to adopt a healthy lifestyle that involves relaxation and adequate diet and sleep, due to the risk of stress-induced relapse of psychotic symptoms. For the same reason, use of other drugs or alcohol should be reduced significantly or stopped altogether.

Regardless of this advice, some people decide to keep using methamphetamine even after they have had a psychotic episode. The following advice could be helpful for such people:

- Avoid injecting or smoking methamphetamine to limit exposure to high doses of the drug.
- Avoid the use of multiple drugs.
- Take regular breaks from using and never use more than twice per week.
- Use no more than a very small amount to limit the chance of another psychotic episode.
- Understand 'reverse tolerance' and the risk of future psychotic episodes.
- Recognise the early warning signs that psychotic symptoms might be returning (eg feeling more anxious, stressed or fearful than usual, hearing things, seeing things, feeling strange or feeling that the world or people have changed in some way etc). If experiencing any of these, immediately stop drug use and seek help to reduce the risk of a severe episode.
- Inform the client that the use of methamphetamine can make prescribed medications for psychosis or schizophrenia ineffective.

Depression

Depression commonly occurs among methamphetamine users, as discussed in previous sections. Symptoms of depression (eg withdrawal from social contact; negative thoughts; feelings of sadness, guilt, pessimism; changes in appetite, libido and energy) may persist for weeks, months or even several years after quitting methamphetamine use.

Encourage clients to be aware of their symptoms and to alert a worker or seek specialist help if depression worsens, particularly if suicidal thoughts occur.

Many workers are reluctant to discuss suicide with clients, but raising the issue will not trigger suicidal ideas in a person who has no intentions. On the other hand, sensitive questioning by a worker can be a relief for clients who have been harbouring thoughts of self-harm, while providing an opportunity for the client to receive the help and support that is urgently required.

A depressed client might be at high risk for suicide if he or she:

- has a clear plan that could cause death and the means to carry it out
- has tried before in the past or recently
- continues to use alcohol and other drugs
- has psychotic symptoms
- has significant life stressors and feels hopeless and helpless to deal with them
- has few or no social supports
- has a family member who has attempted or committed suicide.

The following suggestions from the *PsyCheck* can help guide a worker's response:

Risk level	Action
Low risk: fleeting thoughts of suicide but no risk factors as described above, can guarantee own safety, has supports in place.	• Review frequently. • Identify potential supports or contacts and provide contact details. • Contract with client to seek immediate assistance if fleeting thoughts become more serious or depression deepens.
Moderate risk to high risk: suicidal thoughts present, some or many risk factors, plan has some detail or is very detailed, has means or access to means, poor or no social supports, cannot guarantee safety, feels hopeless.	• Request permission to organise a specialist mental health assessment as soon as possible, continue contract as above, and review daily. • If risk is high and the client has an immediate intention to act, contact the mental health services or emergency mental health team immediately (see *Referral* section below for details) and ensure that the client is not left alone. • Call an ambulance or police if risk is high and the client will not accept a specialist assessment. • Consult with a colleague or supervisor for guidance and support.

Anxiety

Anxiety can occur in many forms and usually involves excessive worry. Other features of anxiety can include agitation, racing heart, sweatiness, rapid breathing or a feeling of breathlessness, tightness in the chest or chest pain, fear or panic, and sleep disturbance.

It is common for methamphetamine users to experience some of these symptoms as a direct effect of the drug. In many cases, anxiety symptoms subside when methamphetamine is no longer used. However, if anxiety symptoms persist after stopping, the client must be assessed by a mental health specialist.

Anxious clients should be provided with a low-stimulus environment and encouraged to take slow, deep, calming breaths. Some useful examples of other relaxation strategies include tensing and relaxing all the large muscle groups in the body; actively imagining a peaceful, safe place of the client's own choosing; taking a warm bath; listening to music; and meditation.

Referring to emergency mental health services

Acute or emergency mental health services usually provide an intake or triage telephone line. Many are staffed on a 24 hours per-day basis in major cities, but in regional areas, emergency treatment is often provided outside of business hours through the emergency department of the local hospital. **Workers should ensure that the emergency telephone number for their most appropriate contacts are on hand at all times.**

A worker should ask the client's permission to contact mental health services. If the client refuses permission, workers can call the local mental health service or the mental health triage worker in the local emergency department and ask for advice about the situation without identifying the client in the first instance.

When contacting a mental health service, give a detailed and accurate summary of the situation and be clear about what the worker's concerns are. Workers should learn to use relevant and appropriate language and only communicate what can be observed. The mental health worker can then offer advice about what to do next.

When a worker telephones an intake officer, the officer will ask for the worker's name, the person's name and the name of the worker's service. The worker will then be asked to describe in detail his or her concerns about the person in question. A worker could state for example:

> *The person is severely agitated, appears to be responding to auditory hallucinations as he is shouting at people who are not present, and he is threatening to harm himself with a knife.*

This will have more impact and convey more information about the situation than for example, *'The guy's going off in the waiting room'***.** In extremely serious situations such as this, the mental health services intake worker will probably instruct the referrer to call the police so the person can be taken to the nearest emergency department or place of safety for an immediate assessment. This is often distressing to both the client and the worker; however, this action is

dictated by the worker's duty-of-care. Workers should also enlist the support and advice of senior staff from their own service in such cases.

Another group of clients might experience serious or lingering symptoms of depression that may lead to thoughts of self-harm or suicide. Workers have a duty-of-care to ensure the safety of clients who disclose thoughts of self-harm. In this case, it is essential to gather as much information as possible before contacting mental health services so the mental health intake worker can make a rapid determination of the client's potential risk and then advise the worker of the best course of action.

Referring for nonemergency mental health assessment

Some clients might have mental health problems that do not appear to pose great risk; however, they may still complicate treatment for methamphetamine use. After gaining consent from the client, the choice of the appropriate contact for a mental health assessment will depend on the location and structure of your service and may include:

- a mental health professional in your own service
- a specialist dual diagnosis consultant
- an intake or triage officer at the client's nearest community mental health service
- a general practitioner or a visiting psychiatrist or clinical psychologist if you are in a rural or remote area where mental health services are not easy to access.

It is important to gather as much information as possible and to use appropriate language when referring clients. Give an accurate description of the person's issues using appropriate language and terms, request an assessment, and indicate what level of involvement in the client's future treatment that you would like to maintain (ongoing contact/counselling, co-case management, etc).

If the client has an established mental health disorder as diagnosed by a psychiatrist, be sure to inform the agency. If not, simply state the client's symptoms or concerns. For example,

> *The client reports feeling anxious and tearful, and her sleeping pattern has been disturbed for several months. She has little appetite, has difficulty managing daily tasks, and although she says she can't imagine going on like this, she says she doesn't have any thoughts of self-harm.*

The assessor or intake worker will then advise the referrer of a course of action, which could include referral to a general practitioner for an assessment or an appointment for an assessment with the mental health service.

Do whatever is reasonable to help the person keep the appointment, but also be sure to maintain professional boundaries with clients. (Also see Chapter 11, *Making links and creating partnerships*).

Recommended service response

It is recommended that each agency or service develop a policy or protocol for identifying and managing mental health problems, including psychosis and suicidal ideation in its particular setting. The document should include the signs, symptoms and management principles listed here, incorporate routine staff education and support, and require prompt debriefing or review should an acute incident occur.

It is recommended that services develop close links with mental health services, ambulance, police and other key agencies so a team approach to response and treatment can be smoothly organised should it be required (see Chapter 11 *Making links and creating partnerships*).

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6
Helping a person get through withdrawal

About methamphetamine withdrawal

Many methamphetamine users will experience what is commonly referred to as a 'crash' or a brief period of recovery when they stop using, which might last for a few days. During this time, the person is likely to experience periods of prolonged sleep, increased appetite, some irritability and a general sense of feeling flat, anxious or out of sorts (dysphoria). As neurotransmitter stores are replenished, the person improves rapidly. It is like a 'hangover' from alcohol. The crash period is not a clinical methamphetamine withdrawal so specialist intervention is usually not required.

In contrast, some dependent methamphetamine users will experience the full-blown withdrawal syndrome when they stop using, the course of which depends on the person's severity of methamphetamine dependence (see Appendix 1: *Severity of dependence scale*); how long and how often the person has used; the presence of other physical or mental heath problems; and other factors such as the setting in which withdrawal is undertaken and expectations and fears about the course of withdrawal.

Signs and symptoms of withdrawal can include:

- a range of feelings from general dysphoria through to significant, clinical depression
- mood swings
- inability to experience pleasure (anhedonia)
- decreased energy
- irritability or anger
- agitation, anxiety
- aches and pains
- sleep disturbance, lethargy, exhaustion, insomnia

- poor concentration and memory
- cravings to use methamphetamine.

Although this varies between individuals, the acute phase of withdrawal can peak around day two or three after last use and generally begins to ease after a week to 10 days. Low-grade symptoms including mood swings and agitation, cravings, and sleep disturbance can last for a further couple of weeks; however, for some individuals, depression can last from weeks to many months or even a year in severe cases.

Withdrawal is most often undertaken at home, but a specialist hospital or residential setting is more suitable for people who are at heightened risk of severe or lengthy withdrawal, have unstable housing, are exposed to methamphetamine at home, or have complicating medical or psychiatric disorders.

Supported withdrawal should be seen as the first step in a comprehensive treatment plan, including counselling and relapse prevention, rather than a treatment in itself.

Assisting a person who is withdrawing

The following strategies are recommended for helping a person who is withdrawing:

- ✔ Tell the person what to expect during withdrawal, including probable time course, common symptoms particularly agitation, irritability, anger, depression, and cravings and possible consequences such as impact on relationships, work, and other social factors.
- ✔ Determine what was and was not helpful during any previous withdrawals.
- ✔ Identify dependence on other drugs and offer appropriate interventions.
- ✔ Recommend adequate diet, rest, and fluid intake. Encourage the person to prepare by having a supply of nutritious food and drink in the house, taking leave from work, limiting visitors etc.
- ✔ Encourage the person to monitor him or herself for symptoms of depression and, if symptoms persist, become severe or thoughts of self-harm occur, advise the person to seek urgent medical attention.
- ✔ Assist with managing cravings to use, by explaining how cravings occur and by developing an early intervention and relapse prevention plan (see Baker et al 2003, *A Brief CBT Intervention for Regular Amphetamine Users*, and Lee et al (2007) for practical strategies for managing cravings).

- ✔ Identify key social supports and educate the family or carers about withdrawal and what to expect (see Chapter 9, *Assisting families, carers and significant others*).
- ✔ Provide written materials as the person may have difficulty with recall and concentration during withdrawal (eg *On Thin Ice,* http://www.ndarc.med.unsw.edu.au).
- ✔ Refer the person to a medical practitioner if the person experiences sleep disturbance or insomnia for more than a week or two, or the person has ongoing feelings of anxiety, agitation or restlessness, which is increasing the likelihood of relapse. Some people benefit from the prescription of a short course of sedative-hypnotic medications such as temazepam for sleep or diazepam for agitation and anxiety.
- ✔ Encourage the person to seek further support if symptoms such as those listed above are severe and persist beyond a week or two.
- ✔ Recommend ongoing interventions such as counselling to prevent relapse to using. Withdrawal strategies should be the *first step* in a planned, individualised treatment approach to support a client's long-term goals.

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7
Use of other drugs and possible effects of mixing drugs

Methamphetamine users often take other drugs in an effort to improve sleep or reduce agitation or anxiety when the person is 'coming down' from methamphetamine. Other combinations provide a pleasurable experience for the user, reflect a dependence on multiple drugs, or are prescribed by a medical practitioner to treat a person's mental health disorder or physical illness.

The risks associated with continued methamphetamine use in combination with prescribed medications **should always be discussed with the prescribing doctor**. However, some clients might be reluctant to disclose methamphetamine use to their doctor for a range of reasons. Workers can assist clients by discussing the issues that are barriers to disclosure and identifying potential solutions together. Sometimes clients need to find a different doctor, with whom he or she can feel comfortable enough to discuss all issues related to their health and wellbeing, including drug use.

Risks associated with prescribed medications

Although the medications described in this section should be prescribed by a doctor, some users obtain antidepressants, antipsychotics and benzodiazepines from other sources such family or friends who have been prescribed these medications, or purchase tablets on the street.

Antidepressants including those that block reuptake of the neurotransmitter serotonin (collectively called selective serotonin reuptake inhibitors or SSRIs), monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants when *used within the same two weeks as methamphetamine* can cause dangerously high blood pressure; increased blood levels of methamphetamine; and serotonin toxicity (overheating, fits, heart attack, stroke, kidney failure).

Antipsychotic medications used to treat psychotic disorders such as schizophrenia can be made ineffective. Methamphetamine can reduce blood

levels of antipsychotic medications, which reduce their effectiveness and lead to relapse of psychotic symptoms. Risk of seizures (fits) also increases.

Benzodiazepines increase the risk of benzodiazepine dependence if large or regular doses are used. Additionally, as methamphetamine use can stop the client from feeling the full effect of benzodiazepines, risk of accident and injury also increases. If clients are injecting methamphetamine, they might also be at risk for injecting benzodiazepines, which can damage veins and cause infections, which can affect the heart (see http://www.druginfo.adf.org.au/article.asp?ContentID = benzodiazepines).

It is important to note that benzodiazepines are very useful in the early stages of methamphetamine withdrawal and are prescribed frequently to reduce agitation and anxiety, and restore sleep. If a client is using benzodiazepines, workers could assist the person to regulate the dosage in the following ways:

- ✔ consider supervised dosing of benzodiazepines (or other medications); for example, a client can receive the prescribed number of tablets each day or once per week from a designated pharmacy, rather than fill a prescription for a month's supply at once
- ✔ reduce the likelihood that the person will obtain multiple prescriptions from more than one doctor (known as 'doctor shopping') by asking him or her to voluntarily complete the *Authority to release personal Pharmaceutical Benefits Scheme (PBS) claims information to a third party* form, which is used to track and monitor prescriptions
- ✔ create a contract stipulating the conditions under which the mediation will be taken (dose, frequency, etc), which the client and worker sign and date.

Blood pressure regulating medication (antihypertensives) can be made ineffective.

HIV medications can result in methamphetamine toxicity (overdose) if taken together.

As new medications are developed and brand names are often subject to change, see the MIMS online website for brand name examples of the medications described in this section http://www.mims.com.au/.

Risks associated with other drugs

Users of methamphetamine typically use a range of other drugs, which is referred to as *polydrug use*.

Alcohol combined with methamphetamine can increase blood pressure, placing greater burden on the heart. It can also stop the person from *feeling* intoxicated or drunk, but the person *is* impaired and blood alcohol levels will still be high. This increases the risk of alcohol poisoning or accidents due to a false sense of feeling sober and in control. (Some people take methamphetamine or other stimulants, because this enables them to drink more alcohol without being sick or passing out.) Use of alcohol and methamphetamine can also place a greater burden on the user's liver, which breaks down alcohol and other drugs for elimination from the body. Careful assessment of a client's use of alcohol will help to identify any problems that the worker should then target specifically (see *Guidelines for the treatment of alcohol problems*, available from http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/AAG07).

Cannabis use has been associated with the worsening of psychotic symptoms in some individuals, particularly those with schizophrenia. People often do not see the relationship as psychotic symptoms tend to worsen a few days after cannabis use. Methamphetamine users with a history of psychosis should be aware of the risks of smoking cannabis.

Opiates increase the risk of heroin overdose, because methamphetamine users may not feel the full effect of heroin and could use considerably more than intended.

Other psychostimulants such ecstasy and cocaine can interact with methamphetamine to increase a user's risk of heart attack, stroke and psychosis.

Tobacco is often smoked in greater quantities when a person is intoxicated with methamphetamine, increasing nicotine-related health risks (eg lung and heart disease, cancer).

Possible interactions with methamphetamine: quick reference list

Drug type	Possible interaction effects
Alcohol	Possible depressed heart and breathing functions
Antidepressants	Possible dangerous rise in blood pressure and body temperature leading to strokes, seizures or heart failure; not to be used within the same 2-week period
Antipsychotic medications	Possible reduced effectiveness of medication, increased risk of seizures
Benzodiazepines	Increased risk of accident and injury and benzodiazepine dependence if taken regularly or in large quantities
Blood pressure medications	Can reduce the effectiveness of medication and increase blood pressure
Cannabis	Linked to worsening of psychotic symptoms in people with psychotic disorders
HIV medications	Increases risk of methamphetamine toxicity (overdose)
Opiates (eg heroin)	Increased risk of opiate overdose
Psychostimulants (ecstasy, cocaine)	Increased risk of heart attack and strokes
Tobacco	Increased risk of lung and heart disease, and cancer

Advice for methamphetamine users

Continuing users of methamphetamine should be provided with the following information:

- ✔ Be aware of the potential interactions of all prescribed medications with methamphetamine, and **always discuss the risks and benefits with the prescribing doctor**.
- ✔ People should not take antidepressants in combination with methamphetamine due to the potential for serious interactions. Users must discuss the dangers with the prescribing doctor.
- ✔ Be aware of the number of benzodiazepine tablets taken as people can lose track. Only take the amount prescribed by the doctor. This will reduce the risk of benzodiazepine dependence and accidents and injuries.
- ✔ Some people can experience withdrawal symptoms if benzodiazepines are stopped abruptly after just one month. Symptoms of benzodiazepine withdrawal can be very similar to methamphetamine intoxication, toxicity or withdrawal (eg anxiety; sleep disturbances; hallucinations; headaches; and depression). The following are hallmarks of benzodiazepine withdrawal and should be attended to immediately if they occur: extreme sensitivity to loud noises, light or touch; feelings of unreality; numbness; fear of open spaces (agoraphobia), a metallic taste in the mouth; pain, stiffness and muscular spasms resulting in headaches and muscle twitching. Untreated benzodiazepine withdrawal can be life threatening because seizures (fits) can occur.
- ✔ Be aware of the amount of other drugs taken (eg heroin) to reduce the risk of overdose. If multiple drugs are taken at once, one drug might 'come one' before another, which can lead to using more of the other drug, possibly taking much more than the person is used to.
- ✔ Be aware of the amount of cannabis used and its effects in combination with methamphetamine, to limit the risk of experiencing or worsening psychotic symptoms.
- ✔ Continuing users of methamphetamine should also be told the following:
  - ✖ Never drive or operate machinery after drinking alcohol and using methamphetamine. Even if the person does not feel drunk after drinking alcohol, he or she is actually drunk, coordination and concentration will be impaired, and the blood alcohol level will reflect this.
  - ✖ Avoid using multiple types of stimulants at once.

References Chapter 7: Use of other drugs and possible effects of mixing drugs

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8
Overview of the range of treatment options

This chapter describes the principles of assessment and the range of treatment options available for methamphetamine users including brief interventions, counselling, behavioural approaches, mutual support groups, residential rehabilitation, and medications. Special considerations for Indigenous clients, youth, and those from culturally and linguistically diverse backgrounds (CALD) are highlighted.

About treatment seeking

As most people feel energetic, confident and euphoric when they use methamphetamine, it is not surprising that many users do not identify as a 'drug user' or do not actively seek treatment until the consequences are severe (eg hostility directed towards a loved one, depression or psychosis, physical health concerns).

Users also report that services are often not targeted to their needs. For example, methadone can be prescribed for heroin dependence, but there are no medications available specifically for methamphetamine use and dependence, although medication trials are currently underway in Australia and elsewhere (see *Medications* section in this chapter).

Research suggests that services generally have a poor record of attracting methamphetamine users into treatment in the first place (engagement) and then keeping them in treatment until goals are met (retention). Engagement and overall outcome are improved by establishing a firm helping relationship and by ensuring that treatment is driven by a *client's* goals rather than those of the service and is matched to the information gained from the assessment (see *Assessment* section in this chapter).

When considering appropriate treatment for methamphetamine users, workers often feel at a loss about how to respond. It is important to recognise that many

of the general approaches undertaken with clients who use other drugs are also relevant and effective for users of methamphetamine. Some useful approaches are described below.

Brief interventions

Brief interventions can be as short as a few minutes in a busy needle and syringe program, through to four one-hour counselling sessions in an outpatient treatment setting.

Brief interventions can include:

- screening and assessment
- provision of self-help materials (see *Resource Section*)
- harm reduction advice
- motivational interviewing
- education
- mood monitoring
- counselling.

Australian research has demonstrated the effectiveness of a brief cognitive behavioural intervention for regular amphetamine users to assist in reducing the quantity and frequency of amphetamine use as well as symptoms of depression. The clinical treatment manual used in the study is freely available (see *Resource Section* for download details).

Assessment

A thorough, routine assessment is undertaken for all clients in most service settings with the probable exceptions of needle syringe programs and drop in centres, for example, where only opportunistic screening or brief assessment is provided. Therefore, most workers in the drugs treatment field should be competent in undertaking a thorough assessment.

Assessments should be offered in the context of a safe, reassuring, supportive, nonjudgmental environment to enhance a client's engagement with the service, which in the early stages, is more important than specific drug treatment. Research has shown that a thorough assessment and follow-up by workers helps some users reduce or stop using amphetamines.

Workers should help clients identify their particular treatment goals (eg cut down or stop using; satisfy a court order; resume or gain employment; regain custody of children; improve a strained relationship, etc). This will help strengthen engagement and assist in the development of a treatment plan that is matched

to individual needs. The worker and client can determine collaboratively the progress of treatment against the identified goals, which can sometimes change during the course of treatment. For example, clients who try controlled use of methamphetamine at the beginning of treatment and find it difficult to maintain might choose to stop altogether.

A thorough assessment for methamphetamine treatment should include the following areas:

- current and past methamphetamine use
- other drugs use
- dependence on each drug
- physical and psychological health
- previous methamphetamine withdrawal
- social factors
- trauma history
- readiness to change.

Each of these is discussed in detail below.

Current and past methamphetamine use

History of current and past methamphetamine use should include the following:

- age at first use
- age at first regular use
- type of methamphetamine currently used (crystal, base, powder, pills)
- route of administration (*How do you usually use methamphetamine?*)
- quantity used (*How much are you using? How much do you usually spend? How many points/grams/etc would you use per day/week/fortnight?*)
- frequency of use (*How often are you using?*)
- when the client last used (*Have you used today?*)
- effects of methamphetamine use on the individual (*How does it make you feel?, Are there any effects that are causing difficulties for you?*)
- potency of methamphetamine used (*How long does it usually last*?).

Other drugs use

Using the questions mentioned above for methamphetamine use, workers should question clients about the use of other drugs. Clients might be unaware of the quantities of alcohol and other drugs that they are using, in which case workers should encourage clients to try to keep track of their use over the next week.

Dependence on each drug

Workers should obtain information about the type and severity of dependence on each drug used. The criteria for dependence on each drug should be determined according to the International Classification of Diseases (ICD-10), which state that a person is considered dependent on a drug if *three or more* of the following apply:

- The user has a strong desire or sense of compulsion to take the drug.
- The user has developed tolerance, ie needs to use more of the drug to get the same effect (*Have you found that you need to use more methamphetamine (or other drug) to get the same effect as before?*).
- The person experiences withdrawal symptoms if drug use is reduced or stopped (*Tell me about when you stop using, how do you feel?*; also see Chapter 6, Assisting a person to get through withdrawal for typical symptoms).
- The person is unable to stop using or is using in larger amounts or for longer periods than intended (*Have you ever tried to stop, but found you couldn't?, Have you ever used more than you meant to?, Have you ever used for a longer time than you meant to for example, did a plan to use for a night or two ever turn into a long binge?*).
- A great deal of time is spent acquiring, using or recovering from the drug *(How much time in your day-to-day life is spent on scoring, using or coming down?*), or important activities of life are reduced or neglected because of drug use (*Do you ever skip or miss important things like work, family, or social events due to using or coming down?*).
- The person continues using despite recognition of persistent physical or psychological harms associated with use (*Do you think that any issues that concern you are related to your drug use? Would you consider stopping because of these issues?*).

The **severity** of dependence should also be assessed (see the *Severity of Dependence Scale (SDS*), Appendix 1).

Physical health and psychological health

Workers should ask about the user's physical and psychological health (*Please tell me about your health in general. Do you have any illnesses or injuries? Do you take any prescribed medication?*).

Sometimes methamphetamine users might not be aware that they have physical problems, so workers should recommend a thorough medical checkup if the person has not seen a general practitioner for some time.

A range of screening questionnaires can be used to assess psychological health (see http://www.adelaide.edu.au/library/guide/med/menthealth/scales.html).

The following questions adapted from the *PsyCheck* package can be useful, and if the person answers yes to any question, a detailed assessment should be undertaken:

- Have you ever had emotional problems or problems with your 'nerves'/ anxiety/worries?
- Have you ever seen a GP, psychologist or psychiatrist?
- Have you ever been told that you have a mental health problem?
- Have you ever been in hospital for mental health treatment?
- Do you take medication?
- Do you feel down, sad or blue?
- Has the thought of harming yourself ever been on your mind?
- Are you more jumpy or anxious than usual?
- Do you see or hear things that other people say they can't?

Previous methamphetamine withdrawal or treatment

Workers should ask about the user's previous history of withdrawal or treatment, including its effectiveness and triggers for relapse (*Have you ever received drug treatment before? What prompted you to start using again?*).

Social factors and history of gambling

- Various social factors should be included, such as information about relationships, finances, legal issues, accommodation, social supports (*Please tell me about your life in general. What about friends and family? Are you in contact with your family? Are they supportive? Are you able to manage on the income you receive?*).
- Information about current or previous history of problematic gambling is also helpful (contact alcohol and drug information services (ADIS) for local treatment services).

Trauma history

Assessment should include information about trauma history, including childhood sexual abuse, torture, critical incidents and war experiences. (*Many people who enter drug treatment have suffered traumatic events in their past. May I ask if that is true for you?*)

If a client discloses a history of trauma and is willing, help him or her access help from a specialist because relapse to drug use is high when trauma-related issues are ignored. Be sure to follow-up the client after the assessment if he or she discloses trauma, particularly if it is the first time (contact ADIS for local treatment services).

Readiness to change

Treatment for methamphetamine use should be matched to the client's stage of readiness to change, which can be categorised as follows:

- precontemplation, where the person is not considering change
- contemplation, where the person has not yet cut down or quit, but is considering change
- preparation stage, where the person has made a firm commitment to quit or cut down
- action stage, where the person has recently cut down or quit
- maintenance stage, where the person has cut down or quit for some time
- relapse, where the person has started to use again.

Harm reduction and brief advice are suitable approaches for those not considering change. Those considering change can benefit from motivational enhancement, education, counselling. Those in the preparation or action stage can benefit from structured counselling, and those in relapse can benefit from motivational approaches and skills building.

Counselling

Formal or structured counselling is usually undertaken after withdrawal symptoms subside and should be provided only by workers who have been trained in the approaches described below (see *Making links and creating partnerships* for advice on referral).

Cognitive behavioural approaches

Cognitive behavioural approaches are the most extensively evaluated of the counselling styles and are effective in helping people address problems with meth/amphetamine use. Several clinical treatment manuals are available to guide clinicians in the use of this approach (see *Resources* section for download details).

Cognitive behavioural approaches are short-term, focused, talking therapies that aim to identify and address common errors in thinking and subsequent behaviours that lead to, and maintain, problematic drug use. These approaches include cognitive behaviour therapy (CBT), mindfulness-based cognitive therapy (MBCT), acceptance and commitment therapy (ACT), relapse prevention (RP), and motivational interviewing (MI).

CBT is also very effective for addressing mental health problems such as depression and anxiety.

The Australian Association for Cognitive and Behaviour Therapy can provide details of CBT practitioners in each area (see http://www.aacbt.org/).

Other counselling approaches

Other counselling approaches include:

- narrative therapy, which emphasises the importance of personal life stories and helps clients determine how their stories shape their thoughts and behaviours (see http://www.dulwichcentre.com.au/NC.Australia.htm for a list of therapists)
- solution-focused therapy, which applies a client's strengths to develop solutions to the problems identified(see http://www.goodtherapy.com.au/find_a_therapist.php for a list of therapists).

Randomised controlled trials of these approaches with methamphetamine users have yet to be undertaken, so their effectiveness is not yet known.

Cost of counselling

Medicare will pay for up to 12 counselling sessions by a registered psychologist endorsed by Medicare if the client is referred by a general practitioner. Some private health funds will cover some of the cost of counselling.

Online counselling for drug and alcohol problems can be accessed free of charge from *Counselling Online* 24 hours a day, 7 days a week, across Australia (see http://www.counsellingonline.org.au)

Community Health Centres also often have counsellors available who can be seen free of charge (see local White Pages or call ADIS for contact details).

The rate for counselling from private psychologists vary, but the Australian Psychosocial Society (APS) recommends fees from $100 for a 30-minute session, through to $360 for a session up to 2 hours (see http://www.psychology.org.au/).

Behavioural approaches

Behavioural approaches help clients alter their behaviours and lifestyles to reduce the risk of using drugs. Behavioural approaches can be used alone or in conjunction with CBT. Behavioural approaches include:

- Avoidance of situations, places or people that have been associated with methamphetamine use in the past.
- Adopting new, healthy lifestyle choices, for example, starting a regular exercise program or engaging in activities like dancing, surfing, diving, skiing, golfing; practicing meditation or yoga.

- Use of distraction techniques to deal with cravings to use (eg going for a walk or run, listening to music, taking a shower, calling a friend, gardening).
- Using contingency management (CM), which is based on the theory that behaviour can be shaped by reinforcement, and both positive reinforcement (reward) and negative reinforcement (punishment) will lead to repetition of desirable behaviours.

Contingency management

American studies have examined programs that provide clients with a voucher that can be swapped for goods (eg food), services (eg accommodation) or cash when they provide a urine drug screen that is free from illicit drugs, or engage in other negotiated and contracted desirable behaviours. The approach appears to be useful in the short term to help people stop using, and it is sometimes used in conjunction with CBT to help people maintain abstinence (see *Reference section* for more information on CM).

Even though this type of CM is undertaken rarely in Australia, workers can apply the principles by providing positive feedback about a client's progress and encouraging involved family members to do the same. Workers can help clients identify improvements in his or her overall quality of life. On the other hand, the risk of relapse is high if the client feels that no improvements have been made. In this case, workers can focus on detailed relapse prevention strategies and help clients identify achievable, short-term goals that can signal progress and strengthen retention in treatment.

Residential rehabilitation

Studies have shown that residential treatment is effective for some users.

Residential rehabilitation (RR) is based on the principle that a structured, longer-term, residential setting provides an appropriate environment in which to address the underlying causes of problematic drug use.

The people who are most appropriate for RR are those who have unstable or no accommodation; have poor or absent social supports; have had repeated failed attempts to cease methamphetamine use in the community; and are dependent on multiple drugs.

RR programs usually emphasise abstinence from all drugs as a treatment goal, and some programs exclude prescribed medications as well. RR programs may involve individual and group counselling sessions; and many are based on a 12-step approach (see next section).

Other RR models integrate various treatment approaches and permit the continued use of prescribed medications for mental health symptoms. This

may be important given that many long-term methamphetamine users also have concurrent mental health problems, and this approach may help address the high initial dropout rates. Workers should understand a RR facility's model for treatment and refer clients to the particular program that will best meet their needs.

Self-help or mutual support groups

Most self-help or mutual support groups are based on the 12-step approach of alcoholics anonymous (AA) or narcotics anonymous (NA), which promotes a disease concept that implies recovery from, rather than a cure for, substance dependence.

This approach is based on the '12 steps' to recovery and includes making a personal inventory of the user's life, making restitution to those injured, and assisting and supporting others through disclosure of personal stories at meetings and personal sponsorship of other users in recovery. It also emphasises a spiritual component or 'higher power'.

A specific group exists for users of methamphetamine known as *Crystal Meth Anonymous*, which is running in some areas of Australia such as Sydney (http://www.sydcma.com/index.htm). Methamphetamine users can attend NA meetings in other areas (see http://www.naoz.org.au/community/index.php for meeting details).

Research demonstrates that some people do well with the 12-step approach although dropout rates are high. Outcomes specifically for methamphetamine users have not yet been determined.

An alternative model, recently introduced to Australia, is SMART recovery (Self Management And Recovery Training), which integrates the self-help, mutual support model with elements of CBT.

The four key elements of SMART Recovery include motivational enhancement, coping with cravings to use, problem solving, and developing a balanced lifestyle. SMART recovery does not have a spiritual foundation and emphasises an evidence-based approach to self-help.

Currently, most groups are run in NSW, although new groups are launched regularly throughout Australia, so check the website for details (http://www.smartrecoveryaustralia.com.au/).

Medications (pharmacotherapies)

Three broad categories of medications are relevant to methamphetamine treatment. These are prescribed to:

- ease the symptoms of withdrawal
- help clients stay off methamphetamine (maintenance therapy or drug substitution therapy)
- treat other disorders such as mental or physical health problems.

Research into the effectiveness of a wide range of medications (referred to as pharmacotherapies) to treat methamphetamine withdrawal and to prevent relapse has not yet demonstrated the superiority of one drug over another because the medications may cause uncomfortable side effects, increased cravings, or lack of improvement in general.

Drug substitution therapy aims to replace an illegal, injectable or smokable drug with a legal drug that can be taken by mouth and to provide an opportunity to stabilise a person's lifestyle enough to allow him or her to receive structured counselling. Substitution with dexamphetamine (a central nervous system stimulant) has been available for some time in the United Kingdom and is similar in principle to prescribing methadone for heroin dependence. Substitution therapy is generally reserved for methamphetamine users who experience the most harm from use.

Medication trials of both dexamphetamine and modafinil, which promotes wakefulness and is used to treat the sleep disorder narcolepsy, are currently underway in Australia.

Evidence suggests that appropriate medications are effective and should be prescribed for diagnosed mental health conditions such as enduring depression, anxiety, and psychotic disorders.

Stimulant treatment programs

Several specific stimulant treatment programs are currently being evaluated in NSW. Treatment comprises assessment and counselling, education, support and specialised treatment for clients who also have mental health issues. Call the local ADIS for details of specific services in other areas.

Other supports

Although evidence is lacking on alternatives to those discussed above, users have expressed interest in complementary therapies and other supports

to improve their general physical and mental health. The following general principles apply to most users:

- A good diet is essential for recovery and long-term health.
- Regular exercise alleviates some symptoms of depression, regulates sleep, and boosts the immune system.
- Meditation reduces stress and improves concentration.
- Massage promotes relaxation.

Special considerations for young methamphetamine users

There is some evidence to suggest that drug use at an early age can increase a person's chances of developing dependence later in life, which is thought to be at least partly due to drug exposure before the brain has fully developed.

Methamphetamine use from a young age has been linked to structural and functional changes in the brains of long-term, regular users later in life.

Rates of amphetamine use among those involved with juvenile justice are higher than that of the general population.

Guidance for working with young stimulant users

Evidence regarding effective approaches for young stimulant users is sparse, although the following can be used as a guide:

- Assessment should include domains described in the *Assessment* section plus exploration of leisure and social functioning, family relationships, peer interactions, hobbies and educational history.
- As with adult users, the intensity of treatment should be matched to the severity of problematic methamphetamine use and associated problems, from the least to the most intensive interventions. For example, a recreational methamphetamine user could benefit from harm reduction advice and education about the short- and long-term effects to reduce risk of regular use or of moving on to injecting. A regular ice smoker with a history of psychosis would need more intensive interventions including monitoring for withdrawal and relapse of psychosis. Treatment matching is known as a 'stepped-care' approach.
- Treatment should be 'youth friendly' and include:
  - follow-up for missed appointments
  - ease of access
  - prompt screening and assessment

  - drop-in capability
  - strong links to other relevant agencies to ensure holistic treatment
  - an environment that is able to provide some basic assistance before the young person enters more formal or structured treatment.
- Family therapy is considered essential in the management of adolescent users.
- Mental health disorders should be assessed and treated appropriately, and a co-ordinated approach should be taken by all workers involved in the young person's care (see Chapter 11, *Making links and creating partnerships*).
- Hospital-based detoxification is rarely required for by young people because of a shorter exposure to the drug and because of a young person's capacity to recover rapidly.
- The Australian Government Department of Education Science and Training has produced a resource *Keeping in Touch: The Kit. Working with Alcohol and Other Drug Use. A resource for Primary and Secondary Schools*, which is useful for those whose work involves schools or school-aged children (see http://www.dest.gov.au/).

Special considerations for Indigenous methamphetamine users

The problems associated with the use of methamphetamine can be even more severe in Aboriginal communities where significant social and health problems already exist. Ideally, both Indigenous and non-Indigenous workers would be available so clients can choose the worker with whom they feel most comfortable. If an Indigenous worker is not available, non-Indigenous workers could seek advice, secondary consultation or other support from Indigenous workers from external agencies, in addition to undertaking training in cultural awareness.

In responding to the needs of Indigenous clients, workers should consider the following issues:

- Culturally appropriate assessment for drug use is required when working with Indigenous clients, and assessment can be enhanced by gaining information from a range of sources including the client, family and other service providers.
- Workers should liaise with other services to establish a strong network that can provide support and follow-up for Indigenous clients (see Chapter 11, *Making links and creating partnerships*).

- Indigenous clients should be informed of how to access additional information (*If you want to know more about (*subject*), this is how you can find it*).
- Careful information gathering is also required to determine the presence and content of delusions and hallucinations. When unusual beliefs or sounds (eg spirits) are described by Indigenous people, workers should not make an assumption that such thoughts are part of the person's cultural beliefs and therefore not a cause for concern. The content of the unusual thoughts should be carefully checked with the person's family or significant others to determine if the beliefs are shared by the person's family or tribe. If the beliefs are *not shared* then they could be psychotic in nature. A declining level of functioning in the person's day-to-day life is also a good indicator that the person is experiencing psychosis.
- Indigenous users may have a higher risk of diseases associated with injecting, including hepatitis B and C. Some evidence suggests that needle sharing is more common among Indigenous Australians than non-Indigenous Australians. This could be due to the culture of sharing among close friends and family, lack of access to clean equipment, or lack of awareness of how to obtain clean injecting equipment. Risks of sharing needles and how to access a supply of clean needle and syringes should be discussed with clients who do not intend to stop using methamphetamine. Workers should encourage the client to consider screening and vaccination.
- Some Indigenous clients may have a low level of literacy, and written materials should be appropriate to the reading age of the client. Other media that are culturally appropriate should be used to deliver harm reduction advice or other information (see http://www.adac.org.au for the comic, *Don't mess with meth*).
- The impact of the person's drug use on his or her family including parenting and child protection issues should be considered. Indigenous families require strong support to understand and navigate the range of agencies that might be involved in their care.
- Methamphetamine use may impose a financial burden, particularly on families that are already struggling.
- Methamphetamine use may alienate the person from family life and cultural activities, and this may affect the client's mental, emotional and spiritual health.

Special considerations for methamphetamine users from culturally and linguistically diverse backgrounds (CALD)

- Research into methamphetamine use in CALD communities is sparse, although drug use is less likely in people from CALD backgrounds than in the wider community.
- People from CALD backgrounds often experience difficulties in accessing culturally appropriate information and treatment services because most services have been developed primarily for non-CALD populations.
- The style of individualised counselling that is provided in mainstream alcohol and other drug treatment agencies may be unfamiliar, and the client and family may lack confidence in treatment outcomes. Workers should carefully explain the aims of treatment and encourage the client and family to recognise even small gains made over time.
- In many cases, cultural appropriateness requires workers to include a client's family in treatment planning, although this will vary from client to client.
- Outreach services and case management approaches are often used by specialist services to respond to the needs of clients from a CALD background.
- An interpreter may be required to ensure an accurate assessment and appropriate management strategy. The use of skilled interpreters with the appropriate dialect and of the client's preferred gender is crucial. Even when families are involved in the client's treatment, it is inappropriate to use family members as interpreters.
- Workers should establish what knowledge the client has about methamphetamine use to begin with and use that as a starting point to provide relevant information and enhance the client's engagement with the service.
- As with Indigenous clients, care should be taken when assessing the nature of possible psychotic symptoms to ensure that unusual beliefs or experiences are not related to the person's culture.
- Workers should explore support needs for any resettlement issues clients from CALD backgrounds might have (eg housing, financial, employment, language, social issues) and help the person access help needed to overcome these additional stressors, which could be a barrier to treatment progress.

General tips for agency responses to methamphetamine users

The following tips will help in responding to the needs of methamphetamine users:

- respond promptly and acknowledge the client's effort to ask for assistance
- be open and nonjudgmental
- provide written resources and advise of the availability of treatment options
- consider the appointment of a case manager and follow up missed appointments
- refer when needed
- provide adequate staff training and supervision.

Each of these is explained in more detail below.

Respond promptly and acknowledge the client's effort

- Develop a culture of prompt response, including telephone response. Be sure to schedule initial appointments, without delay, within 24 hours of the call, even if only an intake or assessment can be undertaken.
- Acknowledge the enormous effort the person has made to ask for assistance — methamphetamine users have often reached a crisis point, and feel low and extremely vulnerable at this time. Workers could say something like 'It must have taken a lot of courage and determination to come here and ask for help'. This recognition can help the person engage with the service and establish a helping relationship between the worker and the client.

Be open and nonjudgmental

- Adopt an open, nonjudgmental, nonconfrontational approach. Accept the client as an individual and do not allow any personal beliefs or feelings about methamphetamine use to cloud the helping relationship. Be willing to work with the client's goals for treatment even if they do not match those of the worker.

Provide written resources and advise of the availability of treatment options

- Ensure that a range of written resources are readily available for clients to take away.
- When amphetamine-specific treatment is available (eg CBT), place signs in prominent positions indicating that treatment is available in the service.

Appoint a case manager and follow up on missed appointments

- Appointment of a case manager can strengthen a client's engagement with the service and help maintain the person in treatment. Case managers also help people access a range of important services from other agencies.
- Follow-up for missed appointments (eg telephoning the client) also increases the likelihood that the client will continue to access the service.

Refer when needed

- Referral information should be readily at hand. However, a client in crisis often does not have the resources necessary to access other agencies, and workers should attempt to address as many of the person's needs as possible in the one setting. If this is not possible, workers should actively help the person access other agencies rather than simply providing 'passive' referrals (see Chapter 11, *Making links and creating partnerships* for referral tips).

Provide adequate staff training and supervision

- Workers should receive regular, relevant training from either more experienced workers within the service or specific training organisations. For example, *From go to whoa* is an amphetamine-specific training package that has been developed for frontline workers. Contact Turning Point Alcohol and Drug Centre in Melbourne for details (http://www.turningpoint.org.au).
- Workers should receive regular clinical supervision in addition to that routinely undertaken by line managers. Supervision provides an opportunity for reflective practice; enhancement of clinical skills; debriefing; maintaining professional boundaries; and attention to the management of stress and burnout. It is also useful for workers to clarify complex issues such as mandatory reporting and mental health interventions. A supervision resource kit can be downloaded from the National Centre for Education and Training on Addiction (NCETA) website (http://www.nceta.flinders.edu.au/csrk/).
- Consider involving peer organisations or individual peer support workers or educators in the service's overall response to methamphetamine users.
- The range of skills and knowledge required by workers to respond appropriately to methamphetamine users include:
  - sound communication
  - engagement and retention strategies
  - screening and assessment for methamphetamine use *and* mental health problems
  - brief interventions
  - risk reduction principles
  - motivational interviewing

  - relapse prevention
  - knowledge of treatment options
  - knowledge of appropriate agencies for referral and strong client advocacy skills
  - CBT or an alternative counselling style if structured clinical counselling is to be offered by the worker.
- Awareness and maintenance of professional boundaries that define the relationship between the worker and client. This can include careful consideration as to what, if any, personal information to share with clients, declining to provide personal phone numbers or addresses, and acting within the parameters of a helpful or therapeutic relationship that is in the best interests of the client.

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9
Assisting families, carers and significant others

Families are often a great source of support and encouragement for methamphetamine users and can be a strong foundation for positive change in their lives. However, family dynamics can also be complex and, in some families, drug use or even violence can be a part of the family system. Workers should explore the family dynamics thoroughly with the client and, if the family situation is unhelpful, it is in the best interests of the client to get support from elsewhere such as friends, peers, and treatment or welfare agencies.

Families should also understand that sometimes users are motivated to protect them from the consequences of their drug use by avoiding their family when they are using, withdrawing or receiving treatment.

In considering these issues, a worker might assist a client who has experienced family breakdown or help supportive families strengthen their relationship with a family member who is using methamphetamine. In some cases, the family or carer *is* the client and the drug user might not be seen by the worker at all. Families of methamphetamine users have needs in their own right, and some services now have a family therapist available.

Tips for helping families, carers and significant others

Regular users of methamphetamine can experience mood swings, anxiety, depression, irritability, anger and hostility. Such adverse effects can have a profoundly negative impact on relationships with family and others. It is often difficult for carers to understand why their family member continues to use methamphetamine in the face of often significant problems related to poor mental health, dependence, finances or the law.

Families, carers and significant others need education, support and practical assistance to help them understand the issues and to improve their own

wellbeing as they maintain a relationship or try to repair a relationship with their family member.

The following suggestions might be helpful:

- ✔ Listen to their concerns, help them clarify the major issues and assure them that a range of feelings such as distress, helplessness, embarrassment, fear and anger are shared by other families and are normal feelings in this situation.
- ✔ Explain the different ways in which people use drugs — experimental or recreational use of methamphetamine does not mean that the user is dependent (see Chapter 1, *About methamphetamine*).
- ✔ Briefly and plainly, describe how this drug works in the body and the range of possible effects. Include information about the 'crash' period and withdrawal symptoms and how regular methamphetamine use can adversely affect a person's mood, concentration and decision-making abilities (see Chapter 1, *About methamphetamine*).
- ✔ Explain the concept of 'readiness to change' to promote an understanding of relapse and how some individuals can be in two minds (ambivalent) about changing methamphetamine use; describe suitable approaches for each stage (see Chapter 8, *Overview of the range of treatment options*).
- ✔ Describe symptoms of psychosis and early warning signs, and recommend an effective approach if the user experiences symptoms. Emphasise that an expression of anger or irritability does not mean that a person is psychotic, but can simply be a sign to back off to allow space for everyone to calm down (see Chapter 5, *Recognising and responding to a person with mental health problems).*
- ✔ Help families develop a crisis plan should the user express thoughts of suicide, develop psychosis or become hostile. The crisis plan should include a safety plan; emergency contact numbers; when and how to enlist the help of specialist mental health services; and how to communicate with the user until help is gained (see Appendix 2 for an example).
- ✔ Explain the range of treatment options available and the role of harm reduction for users not considering change.
- ✔ Explain that there are many ways that a person's methamphetamine use can affect a family. Workers can help families recognise even subtle changes and should encourage the family to develop helpful strategies to deal with undesired changes.
- ✔ Determine what strategies have been successful and not so successful; encourage families to change their approach if it is not resulting in the outcomes they seek.

- ✔ Encourage the family members to be clear about what they will and will not tolerate, to maintain their limits and to communicate this calmly and clearly to the user.
- ✔ Remind family members to look after themselves and not to put their own lives on hold. Stress management, adequate diet, rest and exercise, and continuing to enjoy their usual activities will help family members cope and better enable them continue to care for their family member.
- ✔ Provide information about local support services and encourage families to meet or speak to other families in similar situations (see *Supports for families* later in this chapter). Feelings of isolation and stigma or fears of being judged as a poor parent are common and are often involved in a family's reluctance to seek help.
- ✔ If the methamphetamine user is the worker's primary client, provide as much information as possible to the family without breaching client confidentiality or obtain client consent to provide relevant information to the family.

Dependent children of adult methamphetamine users

Family relationships can become even more complex or troubled when young children are involved. Grandparents and other relatives can be caught between trying to repair relationships with their own adult child or sibling and feeling concern for the children's welfare. Grandparents and other relatives might have difficulty seeing the children if the relationship with their own adult child or sibling is strained. In some cases, grandparents, aunts or uncles find themselves being the primary care giver for the children of methamphetamine users.

In addition to the above, the following suggestions might be useful:

- ✔ Encourage family members to talk to each other about their concerns.
- ✔ If access to children is limited or denied, explore other avenues of maintaining a relationship with the children such as through letters, email or phone calls if possible.
- ✔ Grandparents and other relatives should be clear about what their concerns are in regard to the welfare of the children and, if safe to do so, calmly and clearly discuss this with the children's parents.
- ✔ If the concern for the child's welfare is significant, then the grandparent or other relatives can telephone the state child protection agency and either ask for general advice about the situation before making a decision about how to proceed, or formally report their concerns. Families must be reminded that removal of children from parents is the last resort for these departments — methamphetamine users still love their children and can continue to be good parents.
- ✔ Family members caring for children might be entitled to financial assistance, so contact *Centrelink* for advice.

Young carers

Children and young people are sometimes required to care for or support a family member who has a drug, alcohol or mental health problem. The role that the young person plays will vary from family to family, but can include cooking and cleaning, caring for younger siblings, paying bills, shopping, generally supporting the parent and even intervening during a crisis.

The impact of such a great responsibility can significantly affect the young person's school and social life. The young person might feel isolated, embarrassed, fearful, angry, anxious, and a range of other emotions.

Like older carers, young people need to continue to live their own lives and reduce their stress levels. For example, they could draw, write, listen to music, dance, sleep, read, surf the internet, spend time with friends, or do something physical like playing sport, surfing or riding.

Young carers should also be encouraged to develop a crisis plan should an emergency situation arise. This should include making sure there is at least one trusted person they can contact or stay with in an emergency (see Appendix 3, *Example of a young carer's emergency plan*).

They should also be encouraged to talk about their feelings with a trusted relative, teacher or school counsellor. Some schools now have *Young Carer* support workers and programs available.

Alternatively, they can call Kids Help Line, which is an Australia-wide, free, confidential counselling and support service available to children and young people aged 5 to 25 years. Email or web-based counselling is also available. Telephone toll free: 1800 55 1800. Website: http://www.kidshelp.com.au.

There are several other sites for young carers that have useful links, chat rooms, and practical information available for download: http://www.youngcarersnsw.asn.au; http://www.youngcarers.net.au; http://www.reachout.com.au; http://www.headroom.net.au.

Supports for families

Resources

A Guide to Coping. Support for families faced with problematic drug use. This publication contains personal stories and information about a range of drugs, and offers practical advice to assist families of drug users. The book can be purchased from Family Drug Support. http://www.fds.org.au/

Parent Drug Information Service Information and Support Pack for Parents and Families: For those faced with problem drug or alcohol use of a child or family

member, by the Drug and Alcohol Office Western Australia. This publication can be downloaded from the following site: http://www.dao.health.wa.gov.au/

What parents should know about ice. Victorian Government Health Information website. Brochure can be downloaded in pdf format from the following site: http://www.health.vic.gov.au/drugservices/pubs/ice.htm

Contact numbers and websites

Australia-wide

Family Drug Support is a national, nongovernment support and information service with a chapter in each state that provides family assistance 24 hours a day. http://www.fds.org.au/. Helpline: 1300 368 186.

There is an Alcohol and Drug Information Service (ADIS) in each state, which offers confidential telephone information 24 hours, 7 days a week, advice and counselling services for people with problems related to drugs and alcohol. Each ADIS keeps a complete database of treatment agencies in its state. See contact numbers for ADIS in each state below.

Carers Australia website has many useful links and tips for families http://www.carersaustralia.com.au.

Each state has Al-anon, Nar-anon and Families Anonymous groups. Call your ADIS for local information.

ACT

ADIS: (02) 6205 4545, toll free nonmetropolitan: 1800 422 599.

ParentLink provides confidential telephone information, advice, guidance and referral service: (02) 6205 8800 or http://www.parentlink.act.gov.au/.

NSW

ADIS: (02) 9361 8000, toll-free nonmetropolitan: 1800 422 599.

Family and Carers Support Group, Ted Noffs Foundation: 02 9310 0133 or http://www.noffs.org.au/ (Sydney, Wollongong, Canberra, Coffs Harbour and Dubbo). Programs for parents or carers concerned about their child's drug use.

Parent Line, available 9 am to 4.30 pm AEST Monday–Saturday: 13 20 55.

Northern Territory

ADIS Darwin: (08) 8922 8399, Alice Springs: (08) 8951 7580, toll-free nonmetropolitan: 1800 131 350.

Parentline, a confidential telephone counselling service providing professional counselling and support for parents and care givers, available 8 am to 10 pm, seven days a week: 1300 30 1300 (http://www.parentline.com.au).

Queensland

ADIS: (07) 3236 2414, toll-free nonmetropolitan: 1800 177 833.

Family Drug Support: (07) 3252 1735.

Parent, Child and Family Support Program: (07) 3620 8111.

Queensland Injectors Health Network (QuIHN) http://www.quihn.org.

Parentline, a confidential telephone counselling service providing professional counselling and support for parents and care-givers, available 8 am to 10 pm, seven days a week: 1300 30 1300 (http://www.parentline.com.au).

South Australia

ADIS: (08) 8363 8618, toll-free nonmetropolitan: 1300 13 13 40.

Family Drug Support: (08) 8384 4314.

Tasmania

ADIS Hobart: (03) 6222 7511, toll-free nonmetropolitan: 1800 811 994.

Parenting Line Tasmania: 1300 808 178.

Victoria

ADIS: (03) 9278 8100, toll-free nonmetropolitan: 1800 888 236.

Family Drug Help provides support and information to families and friends of drug users by assisting families and agencies to develop self-help and mutual support groups in their local community: (03) 9572 2855.

Western Australia

ADIS: (08) 9442 5000, toll-free nonmetropolitan: 1800 198 024.

The Parent Drug Information Service (PDIS) is a confidential telephone support service that provides support, counselling, information and referral service 24 hours a day to parents and families in Western Australia: (08) 9442 5050, country toll-free: 1800 653 203.

Grand Care is operated by Wanslea Family Services and is designed to support grandparents who care for their grandchildren. The program offers group and individual support, limited individual consultation and an information line staffed by volunteers during business hours: 1800 008 323. http://www.wanslea.asn.au/services/servicesGC.html.

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Drug and Alcohol Office (2006). *Parent Drug Information Service Information and Support Pack for Parents and Families: For Those Faced with Problem Drug or Alcohol Use of a Child or Family Member*. Drug and Alcohol Office Western Australia, Perth. http://www.dao.health.wa.gov.au/ (Accessed January 2008).

Family Drug Support (2002). *A Guide to Coping: Support for Families Faced with Problematic Drug Use*, Family Drug Support, Leura, NSW.

10
Legal issues

There is a range of legal issues related to methamphetamine use, and key areas are briefly considered here.

Clients who are forced into treatment (coerced clients)

There are times when a person might feel pressured to enter treatment. This is known as *coercion*.

Coercion can be both *formal* and *informal*.

- *Formal coercion* involves treatment that is legally mandated or required to fulfil a court order. The client will be supervised by community corrections, drug courts, diversion programs or similar programs. Clients may also enter treatment to meet requirements of child custody or access rights.
- *Informal coercion* includes pressure to enter treatment from a spouse, parent, carer, other family member, or any significant person in the client's life, and is not bound by legal obligations.

Workers sometimes feel a sense of pessimism about treatment outcomes for coerced clients, particularly those mandated by the courts. However, evidence suggests that treatment is *just as effective for users who are pressured to enter treatment as for those who seek help voluntarily*. Workers must take into consideration that, although the person was coerced to enter treatment, he or she ultimately made the decision to attend.

Careful attention to building rapport, developing an alliance, and enhancing engagement and motivation are important aspects in treatment of the coerced client. Workers should employ a nonjudgmental approach and emphasise that the worker is there to help the client and will respond to his or her needs, and that workers have no role in pressuring or punishing the client in any way.

In responding to the needs of coerced clients, it is important to determine whether the coercion is formal or informal and to target assistance or treatment accordingly. For example, if the coercion is *informal*, client consent is required before any information about his or her progress can be shared with a spouse, family member, significant other or any other party. The extent to which others are involved in a client's care is entirely up to the client even if he or she feels pressured to attend sessions.

If coercion is *formal*, establish a firm working relationship at the outset. Workers should clearly state under what circumstances and to which agencies they are legally obliged to disclose information regarding the client's progress even without client consent (eg diversion programs, community corrections, family services). If workers are unaware of their legal obligations, they should make every effort to find out before the first session is undertaken.

It is also important to note that a longer time in treatment is associated with more positive outcomes for methamphetamine users mandated to treatment; therefore, engaging the coerced client is essential for improving long-term outcomes.

Mandatory reporting

Mandatory reporting relates to legislation specifying who is required by law to report suspected cases of child abuse and neglect.

Every Australian state and territory now has mandatory reporting legislation in place. The information to be reported and the categories of people required by law to report vary across states and territories, so workers have a duty to familiarise themselves with the legislation in their own state or territory. Workplaces should provide an opportunity for workers to understand their responsibilities under this legislation. If ever in doubt about their responsibilities, workers should seek assistance from a supervisor.

Generally speaking, workers are required to report to the relevant state body (eg department of family services, child protection office, department of child safety) if they suspect or confirm that a child or young person is suffering, has suffered or is likely to suffer abuse, neglect or harm. In some states, harm also includes exposure to domestic violence.

Many reports throughout Australia have involved parents who use drugs.

In some states reports can be made before a child is born or shortly after delivery.

For details of specific mandatory reporting legislation, see the Australian Government Institute of Family Studies website for an overview of Australia-wide legislation and for links to each state and territory at http://www.aifs.gov.au.

Crime

A recent survey of Sydney users revealed that many could afford to pay for methamphetamine with a legitimate income, although regular or dependent users were more likely to turn to criminal activity such as drug dealing or stealing to fund continuing methamphetamine use.

There is widespread public perception that all users of methamphetamine are violently out of control. Although methamphetamine users have higher rates of violent offending than the general population, violent crime tends to be limited to a relatively small group of methamphetamine users who are likely to be polydrug users (particularly alcohol and heroin), and who are already inclined toward criminal activity. A single dose of methamphetamine does not inevitably cause a person to become violent.

Violence, when it does occur, is often linked with fear and paranoia associated with regular or dependent methamphetamine use and is frequently triggered in response to a perceived threat, or when a person is paranoid or psychotic. Therefore, hostility and violence are often time limited and tend to occur only when symptoms are acute.

Readers are referred to *Responding to Challenging Situations Related to the Use of Psychostimulants: A Practical Guide for Frontline Workers* at http://www.nationaldrugstrategy.gov.au.

References Chapter 10: Legal issues

Brecht ML, Anglin MD and Dylan M (2005). Coerced treatment for methamphetamine abuse: Differential patient characteristics and outcomes. *American Journal of Drug & Alcohol Abuse* 31(2):337–356.

McKetin R, McLaren J and Kelly E (2005). *The Sydney Methamphetamine Market: Patterns of Supply, Use, Personal Harms and Social Consequences*, National Drug and Alcohol Research Centre, Sydney.

McKetin R, McLaren J, Riddell S and Robins L (2006). *The Relationship Between Methamphetamine Use and Violent Behaviour*. NSW Bureau of Crime Statistics and Research Crime and Justice Bulletin No. 97. NSW Bureau of Crime Statistics and Research, Sydney.

11
Making links and creating partnerships

This chapter provides guidance on developing links and partnerships with a range of agencies and service providers including general practitioners (GPs), mental health services, antenatal teams, police and ambulance services. The different types of referral and tips on improving referral practices are also offered.

Why create partnerships?

Users of methamphetamine are faced with a range of general and mental health concerns, as well as other day-to-day needs. GPs, specialist mental health services (MHS), ambulance services, housing services, employment services, legal aid, and a range of other welfare or support agencies can provide the care and specialist assistance that alcohol and drug treatment services often cannot. The aim of collaboration is to help facilitate timely, appropriate and targeted responses to clients' needs, minimise access barriers for clients, and ultimately improve client outcomes.

Barriers to effective partnerships

Any of the following factors can act as a barrier to developing an effective partnership:

- fear of breaching client confidentiality
- reluctance of some services or agencies to accept or treat known methamphetamine users
- unfamiliarity with the role and function of other service providers or roles in client treatment
- use of different language or jargon

- breakdown of communication or referral pathways, which discourages ongoing collaboration
- workers' lack of awareness of referral pathways and specific roles *within* an organisation.

Tips for developing partnerships

Collaboration can be seen as a continuum, with simple advice or referral at one end to coordinated shared care at the other. Each service should decide the level of collaboration it is hoping to achieve and actively take steps to realise that outcome.

In many cases, collaboration occurs naturally as a consequence of a personal relationship between individual staff members from different services. However, cooperation may stop or change when staff members leave organisations, so formal links are much more likely to last.

Local agencies

The following is a suggested sequence for identifying appropriate local agencies and developing partnerships with them.

1. Identify local agencies

Workers should determine which local agencies could improve their service's response to users of methamphetamine — it is important to find out what potential partners actually offer to make sure the partnership is workable or useful, and that the worker's clients fit the target agency's access criteria before negotiations begin.

2. Meet with the target agency

Workers should approach the target agency with a request for collaboration or cooperation and determine ahead of time how their service could support the partner agency. Workers need to be prepared to outline how their service, the target agency and clients could benefit from a recognised or formal collaboration. Workers might need to challenge some myths that could arise about methamphetamine users (eg all users are violently out of control) and use persuasive client advocacy skills at this stage.

3. Decide on the nature of the collaboration

If the agency is receptive, workers from both services should collaboratively decide on an appropriate level of cooperation, agree on roles, function and outcomes. These might include fast-tracked assessment or access to the other service; reciprocal telephone or face-to-face support or advice; taking turns to provide a regular service to clients in each of the service settings; offers to provide in-service training; sharing of relevant information; co-case management.

4. Consider a joint memorandum of understanding

Consider developing a joint memorandum of understanding (MoU, see Appendix 4 for an example); formal referral pathways; policy and procedures for collaboration including confidentiality and information sharing issues; and timelines for review of effectiveness of collaboration according to the level of cooperation chosen.

The following points relate to developing links with specific services.

Mental health services

The structure of mental health services (MHS) varies across states and territories. Services are provided mainly in the community, and there is now a greater emphasis on collaboration with alcohol and other drug (AOD) services as the overlap between mental health problems and drug use has become increasingly more evident.

Acute MHS undertake assessments of people who are considered a risk to themselves or others. If the risk is high, these people tend to be stabilised in a hospital or acute care setting, whereas those considered less at risk are cared for in the community.

AOD treatment agencies will from time to time contact acute or crisis MHS if workers are concerned about the safety and mental health of a client who is experiencing psychosis or expressing thoughts of self-harm. Similarly, workers will collaborate with community MHS practitioners' if clients with mental health problems receive services from both agencies.

The following steps provide a starting point and an opportunity to develop more formal links.

1. Initiate contact with the MHS

Workers could start by contacting the local MHS with an offer to provide an in-service training session for both community and acute MHS staff members on the topic of methamphetamine use and related problems.

Workers should make contact with the local MHS team that is responsible for assessments (eg crisis team, acute care service, admissions office, etc) and ask for information about their intake procedures, criteria for admission, geographical intake boundaries (usually limited to clients residing in certain suburbs or districts), and office hours, etc so the worker's service can refer clients appropriately.

2. Describe the service offered

Workers could take the opportunity to inform both community and acute MHS staff members of what their service provides; the intake and assessment process; office hours etc, so an understanding of each other's service can be fostered.

3. Develop links with the MHS

If clients with a pre-existing mental health disorder have an MHS case manager, workers should develop cooperative links with the case manager so a collaborative treatment plan can be developed.

In all steps, workers are advised to use appropriate language when referring clients to MHS (see the section *Referring to mental health services* in Chapter 5).

General practitioners

Here are some strategies for establishing links with GPs.

- Start by looking at recent referrals to find which GPs are already accessing the service and who may be willing to become involved in collaboration or shared care.
- Identify whether there is a GP liaison or support person in the local area, because he or she will be working with GPs who are interested in AOD issues. The liaison person might be willing to approach potentially interested GPs on behalf of the service.
- Consider liaising with the local division of general practice to determine if a drug and alcohol or mental health interest group exists and offer to provide an information session on methamphetamine. This is an effective way to make personal contact with GPs to begin a dialogue about cooperation. The publication, *Management of Patients with Psychostimulant Use Problems: guidelines for general practitioners* could be a useful tool (see *Resources* section for download details).

Police and ambulance

The police and ambulance service may be called to provide assistance to workers, so it is helpful to establish a good working relationship with these professionals before a serious situation arises.

- Start by initiating a meeting with representatives from the local ambulance service (some services have paramedics who specialise in drug overdose). This will allow workers to learn about the service; share information; and increase collaboration should an emergency arise.
- If the ambulance workers are not already familiar with resources, introduce them to the publication *Management of Patients with Psychostimulant Toxicity: Guidelines for Ambulance Services*, and offer to provide extra information or support if required (see *Resources* section for download details).
- Contact the community liaison officer of the local police and initiate a meeting to discuss their service, desire for support and prompt response

when required. Offer to provide in-service training or information sessions on methamphetamine or other drugs as required. The publication *Psychostimulants — Management of Acute Behavioural Disturbances, Guidelines for Police Services*, could be helpful as a starting point. (see *Resources* section).

- Consider developing a visiting policy for police to indicate when and where it is acceptable to visit to ensure client confidentiality and continued access of the service. The details could be included in a MoU.

Antenatal teams

- Start by locating antenatal teams by telephoning local hospitals.
- Introduce the workers and the service offered and ask to meet with one or more members of the 'high-risk' team to create a personal link. Inform the antenatal team about what the service offers, and find out what service the antenatal team provides; this information is helpful for both workers and clients.
- Explore the possibility of a shared care role, or at least collaboration, to improve outcomes for pregnant clients.
- Offer to fast-track referrals from the antenatal team to the worker's service for drug counselling/support of pregnant users.
- Offer to provide training for the antenatal teams in methamphetamine or other drug use issues.

Maintaining and improving established links

Workers should establish regular liaison with the target agencies through telephone contact, general practice visits, and informal or formal meetings. This can also include a designated liaison worker if the interaction between agencies is regular.

Offer to provide in-service education to the other agency on topics related to methamphetamine and other drug use, or other topics as required.

Respond promptly to referrals and requests for information or assistance made by the collaborating agency or GP to ensure that communication remains two-way and that collaboration continues uninterrupted and strengthens over time.

Workers should evaluate and revise the partnership if necessary. Evaluation might include the following questions:

- How many clients have been referred to the worker's service by the partner agency? How many clients have actually been seen? Has this number increased or decreased?

- How many clients has the worker's service referred to the partner agency? How many clients have actually been seen? Has this number increased or decreased?
- Have clients of the worker's service experienced reduced waiting time to access the partner agency or otherwise benefited from improved services? Have clients of the partner agency experienced reduced waiting time to access the worker's service?
- Are staff members in both services satisfied with the partnership? Why or why not? Do they have recommendations for improvement?
- Are clients satisfied with the partnership? Why or why not? Do they have recommendations for improvement?

Types of referral

Three different referral practices are outlined below:

- Passive referral — the client is given the name and number of the other agency to make his or her own appointment. This is only suitable for clients who are motivated to ask for help, are not depressed or 'flat', and have the resources to make and keep the appointment.
- Facilitated referral — the worker telephones the other agency, provides basic information, and makes an appointment on behalf of the client. This is probably most suitable for the same group of clients who can receive passive referral.
- Active referral — the worker telephones the other agency in the presence of the client, uses appropriate language to provide detailed information so the client does not have to repeat it at the next appointment, and makes the appointment for the client. This is most suitable for clients who are depressed and or who lack the resources necessary to make an appointment or advocate on their own behalf. Agencies could also facilitate transport to the other service if the resources are available.

Strategies for effective referral

Use of the following strategies can enhance the effectiveness of referrals:

1. Workers address the client's pressing needs first before suggesting referral to another agency for assistance with less important matters.
2. Workers understand the needs of the client, including financial resources; access to transport; requirement for child care; cultural and social issues; level of ability to advocate for self; literacy level; and mental health concerns before making any referral.
3. Workers are aware of agencies that might be of assistance to clients, including location, hours of opening, cost, who is eligible for assistance, and waiting times for access.
4. Workers offer the client a choice of referral points if more than one agency is available to respond to his or her needs.
5. Workers ensure that the type of referral undertaken is the most appropriate for the client, and consent for level of referral is given. The different ways of referring were discussed in *Different referral practices* in Chapter 5.
6. Services involve Indigenous and culturally and linguistically diverse communities in the development of referral practices and pathways.
7. With client consent, workers actively follow up referrals made, to determine if the client kept the appointment and if the agency was able to provide the assistance required. Additional referrals or actions can then be initiated if required.
8. Strong links and partnerships, as described in this section, underpin effective referral processes.

Reference Chapter 11: Making links and creating partnerships

Furler J, Patterson S, Clark C, King T and Roeg S (2000). *Shared Care: Specialist Alcohol and Drug Services and GPs Working Together*. Turning Point Alcohol and Drug Centre Inc, Fitzroy.

Glossary

Abstinence: no longer using a specific drug

Agoraphobia: fear of open spaces

Aneurysm: ballooning of the wall of a blood vessel leading to weakening

Anhedonia: inability to experience pleasure

Auditory: related to hearing (see *Hallucinations*)

Base methamphetamine: 'base' is the street name for methamphetamine that has a damp, oily or paste like appearance

Binge: irregular, on-again, off-again pattern of moderate to heavy drug use

Brain haemorrhage: also known as cerebral haemorrhage, the rupturing of a blood vessel, usually an artery, in the brain (a cause of cerebral vascular accident (CVA), also known as stroke

Bruxism: teeth grinding

Cerebral haemorrhage: the rupturing of a blood vessel, usually an artery, in the brain (a cause of cerebral vascular accident (CVA) — also known as stroke

Coercion: formal (court ordered) or informal (family, spouse, peer, etc) pressure to enter treatment

Cognitive: pertaining to thoughts or thinking processes

Cognitive behaviour therapy: a talking therapy that seeks to modify dysfunctional or distorted thoughts and beliefs

Crystalline methamphetamine: methamphetamine that has a crystalline appearance, which is typically high in purity — street names include ice, crystal and shabu

Depression: a mood disorder or state that meets diagnostic criteria characterised by blunted affect (facial appearance), psychomotor retardation (slowed physical movements and thinking), dysphoria (flat mood) and anhedonia (inability to experience pleasure)

Delusions: fixed, false beliefs that are not amenable to logical challenge

Dependence: characterised by three or more of the following: a strong desire to take the drug, using more than intended, a desire to cut down or quit, using despite harms, increased tolerance, withdrawal

Detoxification: the planned cessation of drug use in someone who is drug dependent

Dexamphetamine: amphetamine that is available on prescription

Dilated: enlarged (eg pupils)

Dopamine: a brain chemical messenger (neurotransmitter) involved in the control of movement, thinking, motivation and perception of reward or pleasure (ie 'reward pathway')

Dysphoria, dysphoric mood: emotional state characterised by discontent, depression, anxiety and malaise

Endocarditis: a bacterial infection of the lining of the heart

Engagement: to attract a person into a service setting; to make a connection with a potential client that will facilitate him or her to actively participate in treatment or the service provided

Euphoria: a strong feeling of wellbeing or elation

Gingivitis: inflammation of the gums

Hallucinations: sensory impression having no basis in external stimulation, can be auditory (hearing), tactile (feeling), olfactory (smelling) or visual (seeing)

Harm minimisation/harm reduction: refers to a range of strategies that aim to reduce harms associated with continued drug use

Hypervigilance: exaggerated preoccupation with external events or people, usually associated with fear of harm

Ice: see *Crystalline methamphetamine*

Illusions: mental impression derived from misinterpretation of an actual sensory event (eg a shadow in a room is perceived as a person)

Insomnia: inability to fall or remain asleep

Intoxication: being affected by a drug

Intranasal: method of administering drugs by sniffing through the nose (snorting)

Lethargy: weariness, lack of energy or stupor

Libido: sex drive

Mandatory reporting: relates to the legislation, which specifies who is required by law to report suspected cases of child abuse and neglect

Methamphetamine, methylamphetamine: amphetamine with the addition of a methyl group on the molecular chain, which gives a potent effect

Motivational interviewing: a non-confrontational cognitive behavioural style of interviewing used to assist clients to recognise and address their health concerns leading to behaviour change

Myocardial infarction: medical term for a 'heart attack', which involves damage to the heart muscle generally through lack of blood supply

Neurotoxicity: injury to the nervous system, death of brain cells

Neurotransmitters: the chemicals that are involved in the transmission of signals from one brain cell (neuron) to the next across a short distance (synapse)

Noradrenaline: a neurotransmitter secreted by the adrenal glands promoting energy and alertness

Over-valued ideas: ordinary events have special significance or are more meaningful than usual

Palpitations: a heartbeat that is unusually rapid, strong or irregular enough to make a person aware of it

Paranoia: mental disorder characterised by delusions of persecution

Pharmacological: relating to the properties or actions of drugs (medications)

Polydrug use: use of multiple drugs

Potency: relating to the level of effect from a specific dose of the drug

Pressured speech: fast, loud and difficult-to-interrupt speech

Psychosis: a mental health disorder characterised by a separation from reality, may include symptoms such as delusions, hallucinations, disorientation and confusion

Psychostimulants: a group of central nervous system stimulants that act to increase the activity of the neurotransmitters dopamine, noradrenaline and serotonin

Recreational use: irregular drug use in a social setting

Regular use: recurring, routine pattern of drug use

Relapse: recurrence of an illness, or return to drug use after a period of abstinence

Residential rehabilitation: medium to long-term treatment option offered in a home-like setting

Respiratory: pertaining to breathing (respirations)

Retention: in this guide retention refers to the maintenance of client engagement with a service, or client participation until identified service or treatment goals are met

Reuptake: reabsorption

Rhabdomyolysis: disintegration of muscle tissue due to very high body temperatures

Route of administration: path into the body by which drugs are used or administered

Seizure: in this guide, a seizure refers to a sudden alteration in motor function, characterised by severe muscle jerking or spasm, and usually involves an alteration in level of consciousness (lay term 'fit')

Serotonin: neurotransmitter involved in complex behaviours such as mood, appetite, sleep, cognition, perception, motor activity, temperature regulation, pain control, sexual behaviour and hormone secretion

Shabu: see *Crystalline methamphetamine*

Sign: behaviour or event that can be seen by an observer

Stepped care: matching the intensity of treatment to the severity of problematic methamphetamine use and associated problems, from the least to the most intensive intervention

Stroke: lay term for cerebrovascular accident involving a blockage of a blood vessel in the brain, which leads to varying degrees of brain damage and possibly death

Subacute: a condition that is not a severe acute condition, and has not progressed to a chronic, long-term state

Substitution therapy: prescription of a drug, which is similar in effects to the illegal drug, which aims to reduce the harms associated with illegal drug use

Suicidal ideation: thoughts or preoccupation with suicide

Symptom: an experience or sensation that is described by the sufferer and often cannot be seen by an observer (contrast with *sign*)

Tactile hallucinations: a hallucination that involves the sensation of touch

Tolerance: a condition in which higher doses of a drug are required to produce the same effect as that experienced when the drug was first used

Toxic: poisonous

Toxicity: the capacity of a substance to produce toxic or poisonous effects

Tremors: shakes, usually of hands, or limbs, can be mild (fine) or severe (coarse)

Urine drug screen: analysis of a specimen of urine to detect the presence of drug metabolites

Withdrawal: the progress and time-course of detoxification

Resources

A wide range of resources about methamphetamine and other psychostimulants are available; the following titles are just a sample:

For workers

Written materials

Australian General Practice Network (2007). *Management of Patients with Psychostimulant Use Problems: Guidelines for General Practitioners.* Australian Government Department of Health and Ageing, Canberra.
http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/psychostimulant-gp

Baker A, Kay-Lambkin F, Lee NK, Claire A and Jenner L (2003). *A Brief Cognitive Behavioural Intervention for Regular Amphetamine Users: A Treatment Guide*. Australian Government Department of Health and Ageing.
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubhlth-publicat-document-cognitive_intervention-cnt.htm (note this website is under review)

Baker A, Lee NK and Jenner L (eds) (2004). *Models of Intervention and Care for Psychostimulant Users — Monograph Series No 51.* Australian Government Department of Health and Ageing, Canberra.
http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-publicat-document-mono51-cnt.htm

Beneath the Ice. A CD ROM for workers, teachers, parents. Purchase details:
http://www.adf.org.au/store/article.asp?ContentID = Beneaththeice725

Lee NK, Johns L, Jenkinson R, Johnston J, Connolly K, Hall K and Cash R (2007). *Clinical Treatment Guidelines for Alcohol and Drug Clinicians. No 14: Methamphetamine Dependence and Treatment*, Turning Point Alcohol and Drug Centre Inc, Fitzroy.
http://www.turningpoint.org.au/library/lib_ctgs.html#14

Jenner L, Baker A, Whyte I and Carr V (2004). *Psychostimulants — Management of Acute Behavioural Disturbances: Guidelines for Police Services.* Australian Government Department of Health and Ageing, Canberra.
http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/psychostimulant-police

Jenner L, Spain D, Whyte I, Baker A, Carr VJ and Crilly J (2006). *Management of Patients with Psychostimulant Toxicity: Guidelines for Ambulance Services.* Australian Government Department of Health and Ageing, Canberra.
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McIver C, Flynn J, Baigent M, Vial R, Newcombe D, White J and Ali R (2005). *Management of Methamphetamine Psychosis, Stage 2: Acute Care Interventions for the Treatment of Methamphetamine Psychosis and Assertive Community Care for the Post-discharge Treatment of Methamphetamine Psychosis*, Drug and Alcohol Services South Australia, South Australia.http://www.dassa.sa.gov.au/webdata/resources/files/Monograph_21.pdf

Websites and useful contacts

Australian Drug Information Network: a government-funded, Australia-wide information, referral, and resource site for workers, clients, families and other interested parties.
http://www.adin.com.au

Australian Government Department of Health and Aging: has a wide range of resources available for download by frontline workers.
http://www.health.gov.au

Department of Human Service, Tasmania Alcohol and Drug Service has on-line facts sheets available as well as information on services throughout Tasmania.
http://www.dhhs.tas.gov.au/services/view.php?id = 354

Drug and Alcohol Services South Australia (DASSA) has on-line resources available for frontline workers as well as details of services in SA and relevant training.
http://www.dassa.sa.gov.au/site/page.cfm

Drug and Alcohol Office (DAO) has on-line resources available for frontline workers as well as details of services in Western Australia and relevant training.
http://www.dao.health.wa.gov.au/

National Centre for Education and Training on Addiction (NCETA) has on-line resources available for frontline workers as well as details of relevant training.
http://www.nceta.flinders.edu.au/

National Drug & Alcohol Research Centre (NDARC) has on-line resources available for frontline workers as well as details of relevant training.
http://ndarc.med.unsw.edu.au/

National Drug Research Institute (NDRI) has a range of publications as well as details of training available in Western Australia.
http://www.ndri.curtin.edu.au/

Next Step Drug & Alcohol Services has on-line resources available for frontline workers as well as details of services in WA and relevant training.
http://www.dao.health.wa.gov.au/AboutDAO/DrugAlcoholServices/tabid/60/Default.aspx

Northern Territory Government Alcohol and Other Drugs Program has information available for workers.
http://www.nt.gov.au/health/healthdev/aodp/aodp.shtml.

NSW Government, NSW Health Druginfo has details of relevant services in NSW
http://www.druginfo.nsw.gov.au/treatment

Queensland Alcohol and Drug Research and Education Centre (QADREC) has on-line resources available for frontline workers as well as details of relevant training.
http://www.uq.edu.au/qadrec/

Turning Point Alcohol and Drug Centre has on-line resources available for frontline workers as well as details of relevant training.
http://www.turningpoint.org.au/

For users

Written materials

A user's guide to speed. National Drug and Alcohol Research Centre
Can be ordered from http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/page/Resources

Crystal meth: reducing and quitting. AIDS Council of NSW (ACON)
http://www.acon.org.au/assets/file_library/other/ACON_CRYSTAL.pdf

Crystal Meth — Effects. Health. Sex. Help. AIDS Council of NSW (ACON). An information booklet for the gay, lesbian, bisexual and transgender community.
http://www.acon.org.au/assets/file_library/brochures/Crystal%20Booklet%20Web%20020051213.pdf

Fast facts on ice. National Drug and Alcohol Research Centre
http://ndarc.med.unsw.edu.au/

Ice: crystal methamphetamine fact sheet. Alcohol and Drug Foundation.
http://www.druginfo.adf.org.au/article.asp?ContentID=ice_crystal_methamphetamine_hy

Ice fact sheet. National Drug and Alcohol Research Centre.
http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/NDARCFact_Drugs7/$file/ICE+FACT+SHEET+2.pdf

On thin ice: a user's guide. National Drug and Alcohol Research Centre
http://ndarc.med.unsw.edu.au/

Websites and telephone contacts

Beyondblue: an organisation that helps people to address problems associated with depression.
1300 224 636
http://www.beyondblue.org.au

Counselling online: is a service where people can communicate with a professional counsellor about an alcohol or drug related concern, using text-interaction. This service is free for anyone seeking help with their own drug use or the drug use of a family member, relative or friend. Counselling Online is available 24 hours a day, 7 days a week, across Australia.
http://www.counsellingonline.org.au

Family Drug Support
1300 368 186
http://www.fds.org.au

Headspace: a government funded youth mental health information site.
http://www.headspace.org.au

Kids Help Line: a free, confidential and anonymous, telephone and online counselling service specifically for young people aged between 5 and 25.
1800 551 800
http://www.kidshelp.com.au

Lifeline: free, confidential telephone counselling service available 24 hours per day, anywhere in Australia
13 11 14

Narcotics Anonymous Australia: information on NA groups and help lines in each state.
http://www.naoz.org.au/community/index.php

Reach Out!: a web-based service that aims to improve young people's mental health and wellbeing by providing support information and referrals in a format that appeals to young people.
http://www.reachout.com.au

SANE Australia: promotes understanding of mental illness through a range of education products and services for those affected, their family and friends, health professionals and the general community.
SANE Helpline: 1800 187 263
http://www.sane.org

SMART Recovery Australia: information on the S.M.A.R.T. recovery approach and location of mutual support groups.
http://www.smartrecoveryaustralia.com.au/

Appendix 1
Severity of dependence scale

(Gossop et al 1995)

1. Have you ever thought your [speed] use is out of control?

Never (0) Sometimes (1) Often (2) Always (3)

2. Has the thought of not being able to get any [speed] really stressed you at all?

Never (0) Sometimes (1) Often (2) Always (3)

3. Have you worried about your [speed] use?

Never (0) Sometimes (1) Often (2) Always (3)

4. Have you wished that you could stop?

Never (0) Sometimes (1) Often (2) Always (3)

5. How difficult would you find it to stop or go without?

Not difficult (0) Quite difficult (1) Very difficult (2) Impossible (3)

Total Score:_____

Note: A cutoff score of greater than 4 indicates severe amphetamine dependence (Topp & Mattick 1997)

Appendix 2
Example family emergency plan

Emergency contact names and telephone numbers

_____

_____

_____

Suicidal thoughts	Psychotic symptoms
High risk if: depressed, discloses a plan that is lethal and has the means or access to the means to carry it out; has tried before; feels hopeless; can't guarantee own safety.	Sees things or hears things others can't; is suspicious or paranoid; has odd or unusual beliefs; behaves in strange or bizarre ways; speech might be disconnected or illogical; might also be anxious, panicky or disoriented.
✔ **DO** be calm, listen without judging, acknowledge feelings, express a desire to help, and determine level of risk. ✖ **DON'T** argue, nag, lecture, or tell them how to 'fix it'. Don't assume that he or she will just get over it or that help isn't required. **If risk is not high but thoughts are present**, encourage the family member to see a counsellor or GP, or telephone a dedicated suicide help-line for support if available. **If risk is high**, do not leave the person alone, do not agree to keep his or her plan a secret, contact the emergency mental health team or call an ambulance on 000.	✔ **DO** be calm, talk slowly, reassure and comfort, acknowledge fears, reduce noise and distractions in the room, call attention to familiar surroundings. ✖ **DON'T** argue, threaten, shout, lecture or laugh. Don't play along with unusual beliefs or ideas. Don't attempt restraint, don't block exits. **Settles?** Continue to reassure, watch carefully and call the mental health service for advice. If psychosis persists call the mental health crisis team or take the person to the local emergency department for assessment (call an ambulance if safety is at risk). **Becomes violent?** Call the police on 000 and enact safety plan.

Safety Plan

Person/service to call first if you feel threatened or in danger:

_____

Place that you (and other family members) will go if you need to leave the house in a hurry (eg *neighbour, friend who lives close by, other relative***):**

_____

Location of extra keys to your house and car:

_____

Other actions:

_____

Appendix 3
Example young carer's emergency plan

Name of young carer:

Phone number(s):

Name of parent or family member:

Name and age of other siblings:

Address:

Emergency contact numbers [insert others here eg kids help line, relative]

000 Ambulance or police

What to say to ambulance officers in case of an emergency:

Other things to do in case of an emergency:

First person to contact if your relative goes to hospital or somewhere away from home:

Name and contact details of person you will stay with:

When staying with someone else, things you should take from home (eg clothes, school uniform, toothbrush, schoolbooks, pocket money)**:**

Other things you need when staying with someone else (eg details of sports practice, a letter to your teacher, transport to school)**:**

Things the person should know about you (eg medications? allergies? doctor's appointments? special food?)**:**

Person to look after your pet:

Person to check on the house while you're away:

When staying at home, the details of help you need to manage:

Person/people to give you this help:

Name and phone number of your local doctor:

Medicare number:

Name and contact number of school:

Support person at school:

Adapted from Young Carers Care Plan, http://www.youngcarers.net.au/

Appendix 4
Example Memorandum of Understanding

MEMORANDUM OF UNDERSTANDING

between

(Insert Agency 1 name here)

AND

(Insert Agency 2 name here)

Purpose or statement of intent

This Memorandum of Understanding (MoU) establishes an arrangement between *(first agency name and description of service)* and *(second agency name and description of service)*.

This arrangement establishes a collaborative relationship between the parties. Each agency recognises that the aims and purposes of the MoU are to *(insert purpose here)*.

Both parties have agreed to enter into this MoU on the terms and conditions contained herein.

Objectives of the MoU

List what the MoU is intended to achieve.

In the operation of the partnership, the parties agree to:

Specify the conditions of the MoU here.

1.

2.

3.

Term of MoU

Insert the duration of the MoU, date of expiry, when and how the MoU will be reviewed, and how it can be terminated before the expiration date if necessary.

Contact persons for MoU

Insert title and contact details for both parties.

Signatories

Signed on this *(insert date)* day of *(insert month)* 20XX.

signed_____

Name and position of authorised person, agency 1

signed_____

Name and position of authorised person, agency 2

UK PARKINSON'S Excellence Network

What drugs might affect the interpretation of DaTSCAN?

Appraised by Kevin Galbraith, 9 February 2016

Update due 2019

Clinical question

In the diagnosis of Parkinson's and parkinsonism, what drugs might affect the interpretation of DaTSCAN?

Background

DaTSCAN is used to detect or exclude dopaminergic degeneration by imaging the dopamine transporter in patients with parkinsonian conditions. Some drugs can have a significant influence on the visual interpretation and/or quantification of DaTSCANs.[1]

Clinical bottom line

1. A number of medications and illicit drugs can interfere with the interpretation of a DaTSCAN. A table below lists some that might often be encountered in clinical practice.

2. The evidence underpinning summaries of such interactions is limited to (i) a guideline that has not clearly followed current procedural guidance, and (ii) a narrative review which constitutes expert opinion (level 5 evidence). The list of interactions derived from these two articles was supplemented for this CAT with those noted by the manufacturer of DaTSCAN (General Electric).

3. This CAT cannot therefore be regarded as a reliable guide to drug interactions that might affect interpretation of DaTSCAN. It does however highlight the need for a rigorously conducted synthesis of primary scientific research in this area

Search terms

(Ioflupane OR FP-CIT OR DaTSCAN OR DaTscan OR DaT-SPECT OR dopaminergic imaging) AND (medication$ OR drug$) AND (interaction$ OR binding OR contraindication$)

Search strategy

Ovid Medline, adapted for Embase and Cochrane Library from 1996 to February 2016. This yielded one relevant narrative review.[1] Hand searching of bibliographies located a guideline from 2010. The guideline[2] is summarised and critically appraised below.

Evidence

A guideline published in 2010 by the European Association of Nuclear Medicine Neuroimaging Committee (ENC) provided procedural recommendations for the use of DaTSCAN, including medications and drugs of abuse that should be avoided prior to the investigation.

Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Kapucu ÖL, et al. EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2. European journal of nuclear medicine and molecular imaging. 2010;37(2):443-50

Summary

The stated aim of the guideline was to: "assist nuclear medicine practitioners when making recommendations, performing, interpreting, and reporting the results of clinical DAT-SPECT studies using 123I-labelled radiopharmaceuticals." The work was guided by the views of several listed national societies: the Task Group Neuro-Nuclear-Medicine of the German Society of Nuclear Medicine, the 'Kompetenznetz-Parkinson' sponsored by the German Federal Ministry of Education, and the Task Group of Neuro-Nuclear Medicine of the French Society of Nuclear Medicine. The guideline included a table reproduced from the narrative review also located in the literature search:[1]

Medications and drugs of abuse which may significantly influence the visual and quantitative analysis of [123I]FP-CIT SPECT studies

Drug class	Drug name	Comments
Cocaine		May decrease striatal [123I] FP-CIT binding
Amphetamines	d-amphetamine, methamphetamine, methylphenidate	May decrease striatal [123I] FP-CIT binding
CNS stimulants	Phentermine or ephedrines	May decrease striatal [123I] FP-CIT binding; influences are likely when used as tablets
Modafinil		May decrease striatal [123I] FP-CIT binding
Antidepressants	Mazindol, bupropion, radafaxine	May decrease striatal [123I] FP-CIT binding
Adrenergic agonists	Phenylephrine or norepinephrine	May increase striatal [123I] FP-CIT binding; influences are likely when infused at high doses
Anticholinergic drugs		Benztropine may decrease striatal binding ratios; other anticholinergics may increase these ratios which will likely not affect visual assessments
Opioids	Fentanyl	May decrease striatal [123I] FP-CIT binding
Anaesthetics	Ketamine, PCP, isoflurane	May decrease striatal [123I] FP-CIT binding; of interest particularly for animal SPECT studies, although ketamine and PCP are sometimes used illicitly

Some additional interactions were described:

- Smoking may interfere with DAT availability, though the effect would likely be too small to lead to misinterpretation.[3]

- Antiparkinsonian medications (such as levopoda, dopamine agonists, NMDA receptor blockers, MAO-B inhibitors and COMT inhibitors taken in standard doses) "do not markedly affect DAT binding and therefore do not need to be withdrawn prior to DAT SPECT."[4] Caution is advised in intra-individual follow-up studies, since downregulation of DAT expression by levodopa cannot be excluded.[5]

A critical appraisal of the guideline was carried out using the AGREE II instrument.[6] Points were noted and scores calculated (between zero and 100%) for each domain as follows:

- **Scope and purpose:** The aims of the guideline were clearly stated, there was clarity regarding the particular aspects of DaTSCAN procedure to be addressed, and the applications of the guideline were very specific. **Score 94%**.

- **Stakeholder involvement:** The guideline was itself guided by the views of several national societies, though the composition of panels from each were not described. There was no mention of patient involvement. The target users of the guideline were clearly defined, as were the particular aspects of practice that would be informed by the guideline. **Score 39%**.

- **Rigour of development:** There was no description of a systematic search for evidence, nor was there any description of criteria for selection of evidence. The strengths and limitations of the evidence were not addressed. There was no explicit method for formulating the recommendations. Some judgement was evident in weighing up the risk of using drugs with minimal effects on DAT binding. There was no clear strategy to link recommendations with evidence, other than the simple provision of bibliographic references. In terms of external review, several international societies were consulted, but the stage at which this occurred in the guideline development process was unclear. No plan was outlined for updating the guideline. **Score 12.5%**.

- **Clarity of presentation:** Few examples were given from each class of drugs. However, the recommendations logically followed stages of the DaTSCAN procedure. **Score 75%**.

- **Applicability:** There was no attempt to describe facilitators or barriers to application of the guideline, no advice on how it might be put into practice, no attempt to address resource implications, and no audit criteria were offered. **Score zero**.

- **Editorial independence:** No information was given regarding funding or competing interests. **Score 25%**.

- Overall, the guideline was rated as of poor quality, with a score of 2 (where 1 = lowest possible quality, and 7 = highest possible quality). The most important limitation was the lack of systematic search and selection of evidence.

In view of these limitations, the particular interactions described in this guideline were compared with those described in the prescribing information provided by the manufacturer of DaTSCAN, General Electric (3.gehealthcare.co.uk). The 'information for physicians' was as follows:

"No interaction studies have been performed in humans. Ioflupane binds to the dopamine transporter. Medicines that bind to the dopamine transporter with high affinity may therefore interfere with DaTSCAN diagnosis. These include amfetamine, benzatropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Medicines shown during clinical trials not to interfere with DaTSCAN imaging include amantadine, trihexyphenidyl, budipine, levodopa, metoprolol, primidone, propranolol and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN imaging and can therefore be continued if desired. Medicinal products shown in animal studies not to interfere with DaTSCAN imaging include pergolide."

Of note is the inclusion of sertraline (an antidepressant of the selective serotonin reuptake inhibitor class) among the medicines that bind to the dopamine transporter with high affinity. This was not included in the guideline.

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Methamphetamine Addiction: A Review of the Literature

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Abstract

Methamphetamine, a synthetically produced central nervous system stimulant, is the second most illicit drug worldwide after cannabis. This drug has an annual global prevalence estimated at 0.4%, and its use is important in North America, Asia, and Oceania.

Literature review was conducted from 1989 to 2011, using PubMed, Google Scholar, EMBASE, and PsycInfo, using the following key words alone or in combination: methamphetamine, addiction, dependence, complications, and pharmacotherapy.

Methamphetamine addiction is a serious public health problem with many consequences and complications. Significant morbidity, including cardiovascular, infectious, pulmonary, dental diseases and other systems complications are associated with methamphetamine acute or chronic use. Methamphetamine dependence also causes serious cognitive impairments that can persist during abstinence and negatively affect recovery outcomes.

There are no approved medications for the treatment of methamphetamine dependence. Efficient treatments include behavioural and psychological approaches of contingency management, cognitive-behavioural therapy, and motivational enhancement strategies.

Introduction

Methamphetamine is a synthetically produced central nervous system stimulant [1]. This drug is the second illicit drug used after cannabis in North America Asia, and Oceania, with an annual global prevalence estimated at 0.4% [1]. Its use remains marginal in Europe except in the Czech Republic (2,8 cases for 1000) and Slovakia (1,5 to 4 cases for 1000) [2]. This drug is usually sold in powder, paste or crystal form. Routes of administration are intranasal sniffing, oral ingestion, pulmonary inhalation, and injection [3]. The effects of methamphetamine use include subjective euphoria, arousal and psychomotor activation [3].

Methamphetamine also known under the street names of "speed", "ice", "crystal", "glass" "meth" or "kryptonite". Dependence is a serious worldwide public health problem associated with major medical, psychiatric, cognitive, socioeconomic and legal consequences. Physiological dependence associated withdrawal-related symptoms and craving are thought to reinforce continued drug-taking, including methamphetamine self-administration [4-6]. If effective public health responses to methamphetamine use are to be implemented, an understanding of the specific harms associated with methamphetamine is necessary. Currently, there is no pharmacological therapy with established efficiency for the treatment of this addictive disorder, and no medications proven to be effective in treating this disorder [7-8].

Literature review was conducted from 1989 to 2011, using PubMed, Google Scholar, EMBASE, and PsycInfo, using the following key words alone or combined: methamphetamine, addiction, dependence, complications, and pharmacotherapy.

Epidemiology

The 2009 World Drug report suggests that up to 51 million individuals (1.2% of the global population aged 15-64 years) have used methamphetamine at least once in the past 12 months [9]. In the United States, data from the 2007 National Survey on Drug Use and Health (NSDUH) indicates that 0.1% of 12-17-years-olds and 0.4% of 18-25-years-olds reported using Methamphetamine in the past month, representing more than 150,000 young users in the United States [10]. While the prevalence of methamphetamine use in the general population is low, rates in younger age groups are significantly higher [11], and life time use of methamphetamine is higher among men than women [11,12]. Methamphetamine use has gained high levels of attention among gay and bisexual men substances users in urban areas [11,12]. In a probability-based survey, approximately 11% of gay and bisexual men in Los Angeles and 13% in San Francisco reported using the drug in the previous 6 months [13]. The popularity of Methamphetamine stems partly from its availability and reasonably low cost, and from disinhibiting effects linked to sexual behaviours [13].

Clinical Pharmacology

Manufacture

Methamphetamine is produced through reduction of ephedrine or pseudoephedrine [14]. Methamphetamine is often mixed with other substances, including caffeine or talc. There are two isomeric forms of methamphetamine, d-amphetamine and l-methamphetamine. The d-isomer is more potent and is the form manufactured for illicit use. The d-isomer form is 80-90% pure [14].

Methamphetamine

Methamphetamine is available in different forms such as a pure crystalline hydrochloride salt or as formulated tablets. Routes of administration are intranasal sniffing, pulmonary inhalation, injection and oral ingestion [14].

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Clinical effects

By its sympathomimetic action-like, methamphetamine accelerates heart rate, raises blood pressure and temperature, and pupil dilatation [14]. Acute methamphetamine use increases positive subjective effects and mood. It removes tiredness and brings a feeling of power, euphoria and self-control [14,15]. Subjective and cardiovascular effects appear to increase depending on the dose. [15].

Withdrawal symptoms

Withdrawal symptoms have been linked to a propensity for a relapse of drug abuse. Dysphoric mood is the main symptom for methamphetamine withdrawal, which requires at least two of the following additional symptoms to establish a diagnostic: psychomotor agitation or retardation, vivid, unpleasant dreams, fatigue, insomnia or hypersomnia, and increased appetite [16,17]. Depressive symptoms vary considerably in intensity and duration, and resolve during the first two weeks of abstinence [18]. Less severe symptoms of withdrawal include anxiety, motor retardation, agitation, vivids dreams, poor concentration, irritability and tension decrease at the end of the first week of abstinence (7-10 days) [19].

The severity of Methamphetamine withdrawal symptomatology, which varies among individuals [20], is likely to influence the ability of MA-dependent patients to maintain abstinence [18].

An understanding of methamphetamine withdrawal may inform on the development of strategies for relapse prevention.

Psychiatric, addictive complications and consequences

Methamphetamine use is associated with a substantial burden of psychopathology, which includes elevated rates of psychosis, mood and anxiety disorders, violent behaviours and cognitive deficits.

Psychosis

Psychosis induced by methamphetamine is a typically transient phenomenon that involves symptoms of delusions, and hallucinations [14]. Methamphetamine-induced hallucinations are predominantly auditory (experienced in 85% of cases of methamphetamine psychosis), visual (46%) and tactile (21%). Delusion of persecution (71%), of reference (63%) and of "mind reading" (40%) are also common [14-21]. There is considerable variability in both the dose required and the onset of psychotic symptoms (7 minutes-34 minutes) [14]. The duration of psychotic symptoms is variable, dissipating within a week of abstinence, or persisting indefinitely [14]. Psychosis can also be accompanied by an emotionally labile state, agitation and hostile behaviour, and can require hospitalisation sedation and antipsychotic medication in severe cases [22]. Psychosis induced by methamphetamine is a transient phenomena remitting rapidly following the stop of consumption [23]. Although vulnerability to psychotic symptoms varies among users, a research reported that 23% had experienced a clinically significant psychotic symptom in the past year and 13% screened positive for a psychotic disorder (compared with 1.2% of the general population) [24].

A number of factors have been associated with an increased risk of developing psychotic symptoms. They are most likely to occur among chronic and dependent users of the drug [24-26]; a study showed that 31% of dependent methamphetamine users had psychotic symptoms, compared with 13% of non-dependent-users [24]. Longer periods of use [23-25], heavier use [24,25], the way of administration (injection) [14], and a pre-existing history of psychotic symptoms increases [21] the risk of psychotic symptoms induced.

Methamphetamine use can precipitate and exacerbate psychotic symptoms among people suffering from schizophrenia [23]. Therefore, Methamphetamine users who have a pre-existing proneness to psychosis are at particularly high risk of experiencing symptoms of psychosis [23].

Depression

Depressive symptoms are common [27]. A recent study reported that a third of methamphetamine users had been diagnosed with depression at some point in their lives [27]. A recent prospective cohort study of young Thai methamphetamine-users found that depressive symptoms decreased significantly among those who stopped using methamphetamine over the 12-month study period [28]. Methamphetamine initiation during adolescence is associated with adulthood depression, whereas early depression was not predictive of future Meth use [29,30]

Anxiety

High levels of anxiety disorders are reported [25,31,32]. Half of methamphetamine users reported symptoms of anxiety prior to initiation, and 75% had experienced severe anxiety symptoms since methamphetamine use [22]. 11% of methamphetamine users have received a diagnosis of an anxiety disorder in their lives [27].

Higher levels of depression, suicide and anxiety have been associated with longer methamphetamine use, early onset, high degree of dependence, frequent use and injecting [24,25,32,33].

Violent behaviours

Violent behaviours appear common among methamphetamine users, particularly among people who inject these drugs [24,25,27], and after methamphetamine use [14]. In the McKetin et al. study, 12% of methamphetamine users had committed a violent crime in the preceding year [27]. Sommers and al. found that more than a third of methamphetamine users had assaulted someone while intoxicated with the drug [33].

Addictive comorbidities

Methamphetamine users consume a variety of drugs. Cannabis use is common, and the majority drinks alcohol. Some have a history of heroin use, and the use of other psychostimulants is common [27-34]. The importance of concomitant use of other substances with methamphetamine is that, when combined with alcohol, cocaine or opiates, methamphetamine toxicity is increased [35,36].

Overdose

Overdose appears to be significant sources of morbidity and mortality among young methamphetamine users [37], and includes agitation, dilated pupils, hypertension, tachycardia, and rapid respiration [14]. Other features include hyperthermia, shivering, dyspnee, chest pain, renal failure, and coma [14]. Elevated risks of overdose among non-injecting methamphetamine users are reported [38]. Those who inject methamphetamine either on its own or in combination with other illicit drugs such as heroin are also at risk of suicide [38,39].

Health Outcomes Associated with Methamphetamine Use

Cardiovascular pathologies

Methamphetamine users are at an elevated risk of cardiac

pathology. Emergency department data has shown consistent chest pain, cardiac arrhythmias (tachycardia), palpitations and hypertension to be among the most common physical symptoms after methamphetamine intoxication [42-45]. A prolongation of the QTc beyond 440 ms is reported among 27.2% of the methamphetamine users [46]. Cardiovascular consequences of methamphetamine use include acute coronary syndrome, acute myocardial infarction, acute aortic dissection, and sudden cardiac death [47]. Cardiovascular complications associated with methamphetamine use can occur with all of the major routes of administration [47].

When methamphetamine is combined with alcohol, cocaine or opioids, toxicity and stress on the cardiovascular system is increased [48].

Cerebrovascular complications

Methamphetamine use is associated with ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage, especially among young patients [49]. A study showed no evidence that the ischemic stroke associated with methamphetamine use is due to an inflammatory etiology but may be due to a process of accelerated atherosclerosis [49]. Methamphetamine leads to increased catecholamine levels, leading to coronary vasoconstriction, production of oxygen-free radicals, myocardial fibrosis, and cardiomyopathie because of the direct toxicity to extra and intracerebral vessels, leading to changes in luminal calibre [49].

Neurotoxicity

Repeated use of methamphetamine involves the degeneration of dopamine and serotonin axons and termini, located in the fronstostrial region, leading to depletion of these monoamines [50,51]. The mechanisms of neurotoxicity are not understood completely, but involve oxidative stress and apoptosis [52-54]. Primate experiments demonstrate that methamphetamine use can lead to neurotoxicity that may require more than a year for complete recovery. *In vivo* human positron emission tomography and magnetic resonance imaging showed brain abnormalities including inflammation [55], reduced neuronal density [55] and reduced density of dopaminergic markers [56-58]. These abnormalities mediate cognitive deficits among methamphetamine users, caused by damages in the cingulated, frontal, and striatal regions [59,60].

Parkinson's disease

Parkinson's disease psychomotor disturbances have been reported among methamphetamine heavy users [61]. To confirm this hypothesis, a retrospective case-controlled study revealed that prolonged use of methamphetamine is associated with an eight-fold increased risk of Parkinson's disease with an average of 27 years between amphetamine exposure and the onset of signs [62].

Neuropschological impairment

Neurocognitive impairment caused by methamphetamine is caused by frontostrial and limbic abnormalities. The main functions altered are learning, episodic memory, executive functions, speed of information treatment, working memory and perceptual narrowing [63]. The cognitive deficits persist over six months after withdrawal [64,65].

Sexual behaviours

Methamphetamine use is reported to enhance sexual pleasure, to facilitate prolonged sexual activity, and to delay and increase orgasm [66,67].

Methamphetamine is used in combination with drugs such as sidenafil to enhance sexual performance [67,68]. The association with others drugs (cocaine, rohypnol) promotes compulsive sexual activity and high-risk activities such as unprotected, anonymous and receptive anal sex among homosexual methamphetamine dependent users [69-72].

Infectious diseases and blood borne virus transmission

Sexual risk behaviour and sharing used needles increase the risk of blood-borne virus transmission (HIV, hepatitis B, hepatitis C) [14]. Methamphetamine-using homosexual men are a high-risk group for HIV seroconversion, because of the high use of methamphetamine among homosexual men who engage in risky sexual practices and those with HIV [73,74]. A study has shown a significantly increased risk of Chlamydia trachomatis infection among methamphetamine-using women [75].

Other outcomes

Studies showed a strong association between methamphetamine use and dental diseases, with a greater number of decayed, missing or extracted teeth among methamphetamine users compared to controls [76]. Others studies reported that teeth grinding [77] and jaw pain [77] and "*meth mouth*"[DDDDD] were more common among the group of methamphetamine users. "*Meth mouth*" is a term used to describe the mouth of a methamphetamine user because of the rampant tooth decay that often occurs with the use of this dangerous drug [78]. Using meth can cause decay so badly that the teeth cannot be saved and must be pulled out instead. Several mechanisms have been proposed (Methamphetamine-induced xerostomia, increased consumption of soft drinks, reduced behaviours) [79], although it is noteworthy that all causal pathways remain hypothetical [80].

Other causes of death

Pulmonary oedema, pulmonary congestion, cerebrovascular haemorrhage, ventricular fibrillation, acute cardiac failure or hyperpyrexia are the main causes of death [14]. Other leading causes of death are related with septic injection or asphyxia by aspiration of vomitus [14].

Pharmacological approaches

Recent improvements in the understanding of the underlying neurobiology of methamphetamine dependence have led to the emergence of promising targets. The adopted strategy has to a large extent resembled the approach to research on cocaine dependence pharmacotherapy, and employed similar preclinical and clinical models [SS]. No substantial evidence for efficient treatment has yet emerged [81]. Clinical trials using aripiprazole [82,83], GABA agents (gabapentin [84,85], baclofen [84], vigabatrin [86,87]), SSRIs [88-90], ondansetron [91,92] and mirtazapine [48-93] have failed to show efficacy [81]. In a double –blind, placebo-controlled design, naltrexon 50 significantly decreased the subjective effects produced by drugs in dependent patients [94]. Trials involving bupropion [8,95,96] and modafinil [97,98] have demonstrated possible benefits in treating methamphetamine use in dependent patients.

The PROMETA protocol, consisting of flumazenil, gabapentin and hydroxyzine, was tested to treat methamphetamine dependence. It appears to be no more than a placebo in reducing methamphetamine use, retaining patients in treatment or reducing methamphetamine craving [99].

Immunotherapies, an innovative treatment strategy of drug

addiction, may be effective in blocking the effects of drug abuse [100]. Preclinical studies have shown the therapeutic potential of the anti-methamphetamine monoclonal antibodies (AMMA) approach [101-103]. Reduction of methamphetamine self-administration, locomotor activity and inhibition of discriminative stimulus effects of methamphetamine was shown in rats and pigeons [104-106]. The two primary indications for the use of AMMA in the treatment of human methamphetamine dependence would be overdose and relapse prevention [107,108].

Conclusion

Methamphetamine is the most abused illicit drug world-wide after cannabis, with about 15-16 million regular users. Methamphetamine addiction is a serious worldwide public health problem with many consequences and complications. Significant morbidity, including cardiovascular, infectious, pulmonary, dental diseases and other systems complications are associated with methamphetamine acute or chronic use. Cognitive disorders, psychotic and mood disorders have been reported. Recent improvements in the understanding of the underlying neurobiology of methamphetamine dependence have led to a number of potentially useful pharmacological agents. There are no approved medications for the treatment of methamphetamine dependence. Efficient treatments include behavioural and psychological approaches of contingency management, cognitive-behavioural therapy, motivational enhancement strategies, and 12-Step programmes [109].

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PATTERNS OF USE AND HARMS ASSOCIATED WITH SPECIFIC POPULATIONS OF METHAMPHETAMINE USERS IN AUSTRALIA - EXPLORATORY RESEARCH (/INTERNET/PUBLICATIONS/PUBLISHING.NSF/CONTENT/PHD-NPI-METHAMPHETAMINE-REPORT-FEB09-L)

6. Specific types of methamphetamine users and behavioural contexts

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6.1 Overview of behavioural contexts and target audiences
6.2 Social use
6.3 Functional users
6.4 Dependent users

6.1 Overview of behavioural contexts and target audiences

When attempting to categorise users, the research found that discriminating factors relate more to behaviour and motivation for use rather than purely demographic factors. While demographic and socio-economic status both play a role, it was apparent that the how, why and when someone uses is better understood through the behavioural context in which drugs are used in addition to the particular methamphetamine(s) one considers using.

This was consistent across all the target audiences specified in the research brief, with the one exception of younger people (16-24 years) living in regional communities. For this group the demographic variables of geographic location and age were a strong indicator of their pattern of drug use. Users in this target audience indicated that methamphetamine use was typically a habitual weekend experience. Boredom appeared to be a key factor contributing to this, with many respondents claiming that they were unsure of what people do on a weekend if they are young and living in a regional community if they did not go out and use drugs. It was apparent that the smaller social networks in these communities resulted in the perception that there is limited choice of social interaction apart from with people who use drugs, and going to venues where drugs are found.

With the exception of this target audience, feedback from the specific target audiences resulted in three distinct behavioural contexts emerging. These included

1. Social Use: motivated by the disinhibitory effects of methamphetamines
2. Functional Use: motivated by the enabling effects of methamphetamines and
3. Dependent Use: motivated by the perception of normality from reliance on methamphetamines.

Table 5 provides an overview of how the target audiences for the research fall into these behavioural contexts. It illustrates how each of the behavioural contexts can be further categorised into more specific behavioural sub-groups. Section 6.2, section 6.3 and section 6.4 discuss these in detail.

Table 5: Target audiences and behavioural contexts

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Table 5 is presented as a list in this HTML version for accessibility reasons. It is presented as a table in the PDF version.

Target audience:

- Young (18-24)
  - Social - blockers **
  - Social - dabblers **
  - Social - Preferrers *
  - Functional - manic Mondays *
- Uni students
  - Social - blockers **
  - Social - dabblers **
  - Social - Preferrers *
  - Functional - slippers *
- Rave partiers
  - Social - blockers *
  - Social - celebrators *
  - Social - dabblers **
  - Social - preferrers *
  - Functional - manic Mondays *
  - Functional - slippers *
- General (25+)
  - Social - blockers *
  - Social - celebrators **
  - Social - dabblers **
  - Social - preferrers **
  - Functional - manic Mondays *
  - Functional - slippers *
  - Dependents - ice zealots **
  - Dependents - meth devotees **
  - Dependents - heroin co-dependents **
- Drivers
  - Functional - workers **
  - Dependents - Meth devotees *
- Construction/labor
  - Social - dabblers *
  - Social - preferrers *
  - Functional - manic Mondays *
  - Functional - slippers *
  - Functional - workers **
  - Dependents - ice zealots *

    - Dependents - meth devotees *
- Hospitality
    - Social - dabblers *
    - Social - preferrers *
    - Functional - manic Mondays *
    - Functional - slippers *
    - Functional - workers *
    - Dependents - ice zealots *
- Rural/regional
    - Social - dabblers *
    - Social - preferrers **
    - Functional - manic Mondays *
    - Functional - slippers *
- Sex workers
    - Functional - workers **
    - Dependents - meth devotees *

Key:

* indicates where target audiences also used in this context, but to a lesser extent.

** indicates the target audience where usage was most prevalent.

6.2 Social use

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Social use of methamphetamines is primarily motivated by the drugs' ability to reduce inhibitions. Users claim to experience enhanced confidence and increased ability or motivation to converse with others. Other key motivations for use include enhanced energy and stamina, alertness and physical senses of touch, smell, sight, and sound. The majority of those using in a social context claim that methamphetamines give an intensity and an ‘edge’ to social experiences, almost allowing them to venture into a different dimension. Used in this context, most social users consider methamphetamines to be 'normal' and 'socially acceptable', although acceptance of specific methamphetamine forms and the frequency of their use vary.

There are common behavioural characteristics that define social users which are distinct from other user groups. Firstly, drug use in this context is always in association with parties, clubs, social events and gatherings which involve other people. In fact, sharing the experience with others is a critical element of the appeal and is often the focal point of the occasion. This is in contrast to other groups where the focal point may be considered the drug itself. For most social users, using alone is commonly frowned upon as this is considered as more consistent with drug dependent behaviour rather than social use.

As a group, social users are also unique because of the parameters they place on their usage. More so than other user groups, social users place definable boundaries around their drug intake to ensure that use is kept under control. These boundaries are defined even more carefully when the methamphetamine being used is ice. The quotes below provide some examples of the parameters that social users place on their drug use:

> *"If I catch myself falling into the trap of doing it multiple days, binges, then I’ll have a break for a few months, just let myself chill and relax and get perspective again, I'm very careful."*

> *"If I start overdoing it I have anywhere up to 6 months break and then I'll start having it again."*

"I don't use everyday and I don't take more than anyone else around me is. It's only to go out on…you'd never do base by yourself…its no fun then".

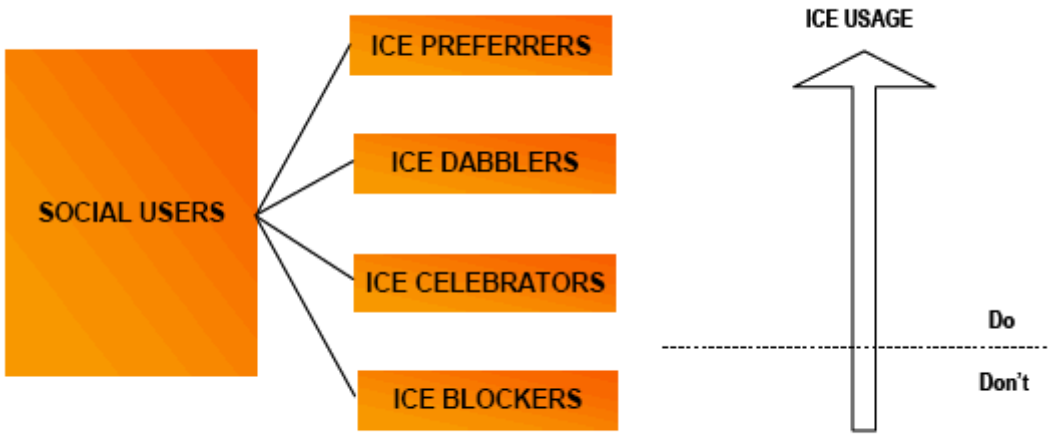
"I'd never take drugs at work".

In comparison to other user groups, social users also appear to place greater importance on maintaining goals and an interest in non-drug activities such as their employment of studies, and in circles of friends who are not regular drug users. They tend to place a greater onus on maintaining good health than other user groups. As long as these self-imposed personal parameters are in place, and use is relatively occasional as opposed to everyday, the consensus is that use of methamphetamines in a social context is relatively low risk.

Types of social users

Social users of methamphetamines are able to be segmented into four distinct sub groups based on their attitudes and behaviour toward ice. Figure 4 shows each of these four sub groups and their relative ice usage. Each is discussed in detail below.

Figure 4: Social user sub groups



Text version of Figure 4

This diagram shows social users split into four groups: ice preferrers, ice dabblers, ice celebrators and ice blockers. Ice blockers do not use ice. The other three groups use ice, with usage increasing from ice celebrators, through ice dabblers, to ice preferrers.

Ice blockers

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Ice Blockers are methamphetamines users who do not use ice. While they are motivated to use other methamphetamines in a social context for the effects described above, Ice Blockers make a conscious decision not to use ice. While drug use may still be as frequent as every weekend or fortnight, this group's preference is for what they perceive a 'safer' repertoire of drugs. Most commonly, this includes speed, base, ecstasy (commonly known as pills among methamphetamine users) and marijuana. To a lesser extent, LSD and magic mushrooms are also used.

For Ice Blockers, the comparative potency and associated risks are considered to be leagues apart from other methamphetamines, so much so that its benefits are not perceived to outweigh potential risks. There is a fear around ice-taking, which cause this group to abstain from use. This fear is based on either one of two things:

- The fear of side-effects from using ice, particularly those highlighted in the recent ice advertising campaign. Ice Blockers with this fear consider ice 'evil' or the 'monster' drug or
- The fear of the irresistibility of ice, whereby Ice Blockers consider ice as 'so good, it's bad'.

The first of these fears is typically found among younger methamphetamine users aged 16-24 years, who are usually students and rave party attendees. This group have not tried ice before. Their fears are often based on things they have seen in the media, in advertising and stories heard through friends, rather than personal experience. Often these are specific side effects such as uncontrolled scratching, the potential for immediate addiction, and possible psychotic episodes. However, their fear can also be more generalised, relating both to the social stigma that the general community is believed to associate with using ice, and the potential for the intense effects of the drug to cause them to behave in a way which results in social disgrace among peers. While most are adamant they would never try ice, they claim to regularly use other drugs such as speed, base and pills.

In contrast, those that fear the irresistibility of ice are typically older users (25+ years), commonly including professionals, older ravers and gay, lesbian and bisexual users. These people have usually tried ice before in a social context, and subsequently believe the increased potency and effects of the drug are appealing enough that they could potentially become addicted if given further opportunity to use.

> *"It's like super speed. You can just see the potential addictiveness when you take it, so to me it's like 'oh no stay away from it'."*

For these Ice Blockers it is the fear of losing control of their ability to manage their drug use that prevents them from using ice. They believe that if they lost control over their use, they would become exposed to the long term risks that are considered to be inevitably associated with any drug addiction. This belief strengthens their resolve not to use ice again. Instead, Ice Blockers who fear the irresistibility of ice also limit their drug usage to speed, base and pills.

Ice dabblers

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Ice Dabblers use ice opportunistically. That is, while ice is neither their drug of choice nor a drug they proactively seek, they will use it on occasions when it is offered by others. For this sub group, the motivations for use of ice are primarily peer driven and centre around a desire to be on 'the same level' and sharing the same experience as their friends.

> *"I would use it if someone offered it to me but I would never buy it."*

> *"The night is about being with my friends so I'm happy to take whatever they're having so that I can be on the same level and share the experience".*

Ice Dabblers encompass a range of target audiences, most commonly ravers, gay, lesbian and bisexual users, hospitality, university students and people from rural and regional areas. This group includes both young and old users and people with a range of occupational aptitudes from skilled, semi-skilled and unskilled working categories.

Attitudes toward drug taking among this group tend to be somewhat laissez-faire. If the drug is perceived as coming from a known, trusted source, most are receptive to taking almost any drug socially. Heroin is perhaps the only exception to this. Pills and speed are usually preferred by this sub group, partly due to the ease of administering when in public, although many claim to also use base relatively regularly. Ironically, many Ice Dabblers have a low regard for ice compared with other drugs. However, unlike Ice Blockers, when faced with the opportunity to use it among peers, they typically find it easier to submit rather than resist.

> *"You try and stop yourself and you try and stop your friends from getting involved in it but sometimes it just creeps into the circle and you find yourself taking it."*

Given their relaxed attitude to drug taking, it was not surprising that poly drug use is very common among Ice Dabblers. On any

given night out, often a mix of drugs are taken. This mix may or may not include ice, depending on availability and social company. For a minority, when ice does feature, its inclusion may be a main focus of the night with use occurring at a house party or even before going out to pubs or clubs. However, for most of this social sub group, when ice is used it is often introduced during the later stages of the evening at someone's house after leaving a dance venue or club. When asked to describe how ice is used, this social sub group often reported behaviour that was similar to that described below:

- speed before going out
- followed by one or a number of pills once out
- then additional speed later in the night to enhance and sustain the effects of the pill
- for some, alcohol may also be consumed throughout the stay at the venue, although this can depend on the venue and tended to occur less at venues such as raves and then
- a smaller more intimate group of friends would return to someone's house for a 'kick on' / or 'come down party'.

It is at this latter stage, that marijuana and ice are most likely to feature. Which of the two drugs used appears to depend on availability and the intended length of the party. Use of ice will ensure that party continues much longer than if marijuana is used.

Frequency of methamphetamine use for this sub group depends on the age and social interests of each individual. Similarly, whether they use ice or not will depend on age and social interests. Some follow a poly drug use pattern such as that described above as frequently as every weekend, while others only do so once every 6-12 months. Depending on the drug and the users' personal preference, the most common forms of administration of methamphetamines among this group include either snorting, ingesting or smoking.

In comparison to other drugs, Ice Dabblers only use ice occasionally. For some it is limited to only one or two previous experiences. Despite this, it is important to recognise that the low frequency of use among this group is usually a consequence of limited exposure, rather than an act of will or discipline. That is, the limited use of many Ice Dabblers is due to external reasons such as infrequent social contact with their 'ice' circle of friends, limited availability among their peer group, or infrequent attendance at 'kick on' parties where ice is most likely to be available.

Ice celebrators

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Ice Celebrators are those social users that consciously limit their ice usage to special occasions. Based on the drug's increased purity and potency, Ice Celebrators regard ice as a more 'exclusive' drug experience, and claim to have respect for its effects, both good and bad. While they may or may not use other drugs on a regular basis, they typically limit their ice intake for special, infrequent occasions such as all-weekend rave events, special birthdays, certain festivals, weddings, New Years parties and so on. Their ice intake is usually planned ahead of time, and unlike many other occasional users, Ice Celebrators typically initiate the purchase rather than rely on the drug being offered to them.

This sub group are typically older (25-35 years), and include professionals, gay, lesbian and bisexual users and older ravers. Most Ice Celebrators have been attending the 'rave scene' for many years, and generally have a relaxed attitude toward drug taking in this context.

The frequency with which Ice Celebrators use other methamphetamines is strongly dependent on their existing active interest in clubbing and raves. Frequent clubbing appears to correlate with higher use of speed and base, while infrequent use typically relates to users tiring of the rave 'scene'. Some Ice Celebrators claim to now only use drugs infrequently, for example, every 6-12 months. In these instances, ice is often the only drug they would use.

Ice preferrers

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Ice Preferrers are the social users who claim ice as their drug of choice. While other drugs may be used occasionally, ice is the primary drug they seek for use in a social context. Ice Preferrers are categorised by their preference of ice being based on the potency of the drug due to its purity and the intensity of experiences this provides. This is in direct contrast to other social user sub groups, who are either frightened of the intensity of the purity and experiences (Ice Blockers), or

simply prefer the lower intensity of other methamphetamines (Ice Dabblers). Ice Preferrers differ from Ice Celebrators in terms of perceptions of suitable occasions for use. For Ice Celebrators the drug's potency and intensity is why it is saved for special occasions. For Ice Preferrers, these characteristics are why they use it for any social occasion. Many claimed to have moved to ice from a previous preference for speed and see it as providing better value for money than other methamphetamines. These unique motivations are illustrated by the quotes below.

> *"Ice has killed speed now because it's the same thing but so much more effective".*
>
> *"The hit just seems cleaner than the other drugs".*
>
> *"You get more bang for your buck".*

Ice Preferrers are typically older, with a greater frequency drug use. They are from a range of occupations, encompassing professionals and unskilled workers and include the gay, lesbian and bisexual, general users aged 25 plus years, and older regional and rural target audiences. University students and ravers are less common in this social sub group than others.

Unlike other social users, Ice Preferrers' social interests are not about going out, dancing and meeting new people. This may be due to the relative unavailability of clubs and rave parties, for example in regional and rural areas, or due to undesirability with users feeling they have out grown the club or rave scene. For this sub group, the focus of the social occasion is in enjoying intense conversation and shared experiences with an 'inner circle' of friends. A house party with close friends is a typical context for use. Circulating the ice pipe is often an essential part of the shared experience, and carries the same sense of social interaction as passing a joint[17]. Many claimed that smoking ice in this context often continues throughout the night and into the next day.

As it is their drug of preference, Ice Preferrers usually have some on hand. This results in increased frequency of ice use in comparison to other social user sub groups. Ice Preferrers typically claim to use the drug weekly, or at least fortnightly.

> *"Most Fridays we'll have a few friends come over and we'll just sit around smoking and drinking, playing some music".*
>
> *"I may smoke on and off throughout the weekend with my partner, or when people drop by".*

While smoking is the most common route of administration for Ice Preferrers, a minority prefer to either inject or snort, preferring the longer, more fulfilling high.

> *"Smoking it is just so wasteful, you always need more".*

Summary of social user sub groups across target audiences

Table 6 summarises which of the target audiences are more prevalent in each of the four social user sub groups described above.

Table 6: Summary of social user sub groups across target audiences

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Table 6 is presented as a list in this HTML version for accessibility reasons. It is presented as a table in the PDF version.

Summary of social user sub groups (blockers, celebrators, dabblers and preferrers) across target audiences:

- Young (18-24)
  - Blockers **
  - Dabblers **

- Uni students
  - Blockers **
  - Dabblers **
- Rave partiers
  - Blockers *
  - Celebrators *
  - Dabblers **
- General (25+)
  - Blockers *
  - Celebrators **
  - Dabblers **
  - Preferrers **
- GLBT
  - Blockers *
  - Celebrators *
  - Dabblers **
  - Preferrers **
- Drivers
  - n/a
- Constructions/labour
  - Dabblers *
  - Preferrers *
- Hospitality
  - Dabblers *
  - Preferrers *
- Rural/regional
  - Dabblers *
  - Preferrers **
- Sex workers
  - n/a

Note: * indicates less prevalence

** indicates greater prevalence.

For each target audience, if a sub group is not listed indicates little or no apparent representation of target audience in the behavioural sub group.

6.3 Functional users

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Functional use of methamphetamines is primarily motivated by the enabling effect of the drugs. Achieving a certain task is what use in this context is based upon. Most often, this refers to functioning in employment. In this context, methamphetamines are used to enhance confidence, alertness, concentration, motivation, energy and stamina, or suppress appetite and lose weight. Increases in one or all of these characteristics effectively enable the user to achieve the task more quickly or with greater thoroughness.

Attitudes of functional users to methamphetamine use differ markedly to that of social users. While social users readily recognise the illicit nature of their drug use, functional users are less inclined to. Those who use in this context self-permit methamphetamine use by justifying it as a 'means to an end'. Further, many functional users are reluctant to see themselves as drug takers, particularly the more regular users. Instead, many see themselves as workers simply trying to get the job done or people with a goal to achieve.

Feedback from the research suggests the prevalence of methamphetamine use in a functional context at the workplace is relatively widespread. Not only was it claimed to be used in many unskilled or semi-skilled roles, such as trades and construction, labouring, driving, hospitality and sex workers but also in more professional roles such as IT, management, finance, and in the area of health. University students can also be included in this behavioural context when using to study or to complete assignments to meet a deadline. Drug use in this context is considered acceptable, and in small number of cases, even expected:

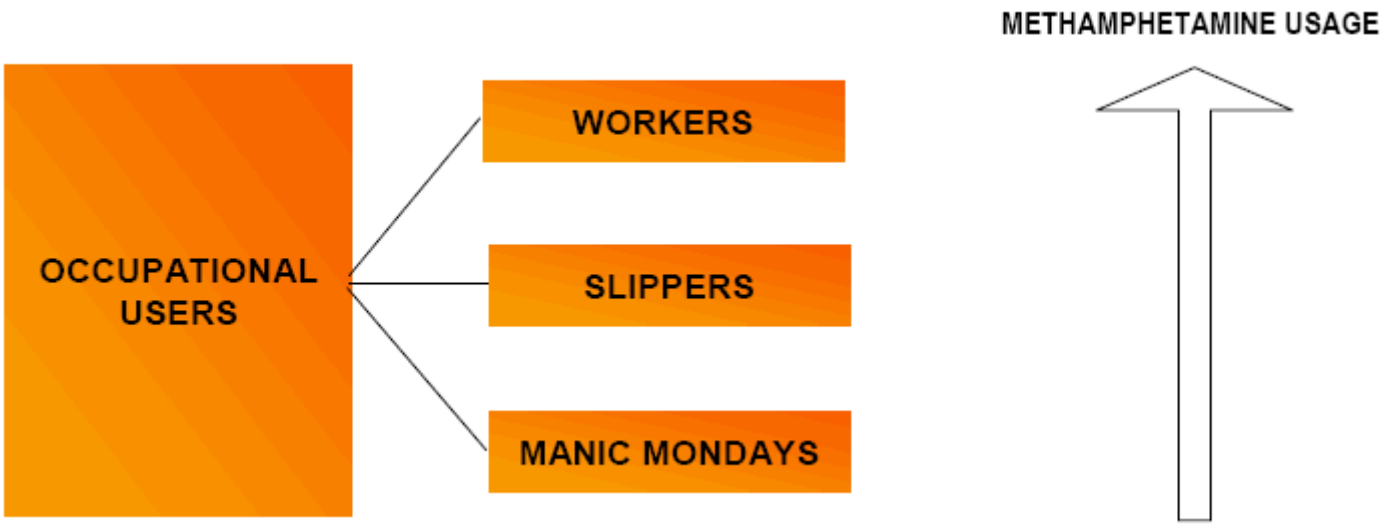
> *"A lot of people at my work do use drugs but we don't have drug tests so it's fine"*

Speed and base are the common choice of methamphetamine used in this behavioural context. The longer lasting, lower intensity effects of the these two drugs compared to ice, mean they are considered more suitable for tasks of longer duration such as a day labouring, long periods of time spent driving or concentrating on details. Although not as common as speed or base, ice is used in a functional context particularly by those who require a more intense effect over a shorter period of time. For example, some sex workers found ice useful for the increase in stamina and disinhibitory effect that it produced over the short term. A minority of other functional users used ice rather than speed or base as it was their drug of preference socially, so it is usually readily available.

Types of functional users

Like social users, sub groups of functional users were able to be identified. Although similar in many ways, sub groups of functional users were able to be differentiated according to levels of use and attitudes toward methamphetamine usage.

Figure 5: Functional user sub groups



Text version of Figure 5

This diagram shows occupational users split into three groups: Workers, Slippers, and Manic Mondays. Methamphetamine usage increases from Manic Mondays, through Slippers, to Workers.

Manic Mondays

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Manic Mondays are social users who have experienced a lapse in discipline. This user group can encompass any one of the target audiences involved in the social use of speed or ice. Target audiences that regularly use methamphetamines to go out to a venue or club, such as gay, lesbian and bisexual users, ravers, young people, university students, hospitality workers, labourers, and those from regional and rural communities are particularly susceptible to falling into this category. However, this functional sub group was most prevalent among general users aged 25 years and over.

The key difference between the Manic Mondays sub group and social users is that they have allowed themselves to break one of their own rules of not using at work, and have let their weekend drug use flow into the first day of their work week. While this is typically a Monday, it could be also be a Tuesday or Wednesday for groups such as hospitality workers or students.

Manic Mondays still have a social user's attitude to drug taking, that is, it is very much a social activity to do with friends to enhance the social experience at a club or house party. However, occasionally, when the social occasion has lasted longer than normal - "a big weekend" - Manic Mondays allow themselves to use in the morning before work rather than call in sick. Essentially they are compensating for not limiting the amount of partying or drug taking that occurred on the weekend as social users will do.

This sub group fear taking methamphetamines at work for a number of reasons. They fear being caught by their employer and potentially losing their job. Further, they believe that once a person starts using regularly at work, they are at risk of becoming dependent. For these reasons, functional use in this context was claimed to be very rare. When it occurs, it is considered an absolute 'necessity':

> *"I would never normally take drugs on a Monday, but I'd barely slept the night before so I needed something to keep me awake".*

Slippers

Slippers are functional users who regularly use methamphetamines to get through the working day or a specific task. Usually they are workers or students who use drugs to help them function throughout their working or study week in addition to social use on weekends. Typically, they evolve from Manic Mondays as their attitudes and behaviours have become more comfortable with regular, mid-week use after having taken once or twice at work as Manic Mondays with no repercussions. Despite being aware of some of the immediate risks and effects of methamphetamine use, Slippers believe they function relatively normally in this state and inadvertently place themselves at risk of becoming more regular functional users.

Slippers usually encompass the same target audiences as Manic Mondays, although some other groups fall directly into this category. Some university students regularly use methamphetamines to enhance their energy and concentration for study and assignments. These students will actively seek out methamphetamines specifically for this reason, rather than simply to recover from using them the night before. A small number of respondents, usually women, were also identified to fall into the Slippers category as their primary motivation for using methamphetamines was to suppress appetite and lose weight. As stated by one:

> *"I've been on a meth diet this week, trying to lose weight for my holiday"*

A number of Indigenous women claimed weight loss as the primary motivator for beginning to use methamphetamines in the first place. They claimed that this was often at the encouragement of their friends or family.

Speed and base, or drugs like dexamphetamine are the preference for functional users in this sub group. Ice may be used on the odd occasion, depending on what was taken the night(s) before and is available on hand, but it was not uncommon for some Slippers to avoid ice altogether due to a fear of the risks and potency (typically younger/ university students). Others may dabble in ice socially, but its use was not perceived as appropriate in a functional context, due to the intensity of the high is making it difficult to concentrate. Further, the length of the comedown experienced when using ice defeats the purpose of having to use

drugs to get through the day. The quotes below illustrate the preference of Slippers for speed and base:

> *"(speed is) a longer hit, and not as high, so at least you can still function properly".*

> *"I'd never do speed or ice at uni, but a couple of dexies is nothing to help me get through".*

The typical routes of administration for methamphetamines in this context is snorting, smoking, and ingesting. Rarely are they injected.

Workers

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Workers stand apart from other functional groups. This sub group uses methamphetamines almost exclusively for functional reasons, usually improving performance on the job, rather than as part of a social interaction. The key distinction between Workers and other functional user groups is that they are more self-permitting of their own usage behaviour. They are also more frequent users.

Workers are the least likely of all the functional sub groups to consider themselves as illicit drug users. Unlike other sub groups, their drug use is a 'necessity' for keeping their job, not as something that could potentially cause job loss. The research found that functional use in this context was more prevalent in certain industries, particularly those requiring heavy or continuous labour, late shifts or long hours. Some examples of the occupations of respondents that fall into the Workers category include construction, truck and taxi drivers, road workers, sex workers, dancers and hospitality workers, and trades such as plumbers and electricians.

> *"There's no shortage of workers, and so many of them are much younger, stronger and faster than us older blokes. I need the extra strength (drugs) give me, otherwise I'm without a job" (construction worker).*

Anecdotal evidence suggests that a small minority of employers accept, and even encourage, drug use. Often, however, it is still an unspoken behaviour within the workplace. The quotes below provide some examples of functional use as an expected part of employment.

> *"I know a site where it's common knowledge the boss actually puts speed in the water to get all the blokes to work faster" (labour worker).*

> *"The boss knows what's going on. There's no way we could meet his deadlines without (drugs)" (truck driver).*

Base or speed are usually the preferred methamphetamine used by Workers, partly due to ease of administration. White powder can be easily scooped onto a finger, or other device such as a door key, and snorted, ingested or sprinkled in a cigarette. Both powder and paste (base) easily stirred into water.

The other reason while these forms of methamphetamine are preferred is due to the more consistent, sustained high they provide. This makes them more appropriate for longer shifts lasting 6-8 hour shifts. A small number of sex workers and dancers were the only exception to this preference. For this small group, ice was preferred for the more intense, more disinhibitory high it provides over a shorter period of time. In this instance, the route of administration tended to be smoking or injecting.

Behaviours among Workers often border on dependency with use being frequent and sometimes continuous, over comparatively longer periods. This could be anywhere from 4 to 7 days in succession depending on the role. In order to avoid the effects of the comedown, drug use may unintentionally carry over to time spent outside of employment, such as the weekend or day off.

Workers in industries where employment is short term contractual or where there is a high degree of competition for roles, such as labouring and construction, often feel trapped into continued use. Even if they are consciously aware of their increasing reliance on drugs, they perceive that stopping use will require taking time off to detox. This in turn means no or low productivity

and potential loss of job, resulting in financial problems. Other Workers in competitive employment or more flexible roles, such as some drivers and self-employed professionals, claimed they control the habit through self-imposed detox breaks every few days.

Summary of functional user sub groups across target audiences

Table 7 summarises which of the target audiences are more prevalent in each of the three functional user sub groups described above.

Table 7: Summary of functional user sub groups across target audiences

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Table 7 is presented as a list in this HTML version for accessibility reasons. It is presented as a table in the PDF version.

Summary of functional user sub groups (manic Mondays, slippers and workers) across target audiences:

- Young (18-24)
  - Manic Mondays *
- Uni students
  - Slippers *
- Rave partiers
  - Manic Mondays *
  - Slippers *
- General (25+)
  - Manic Mondays **
  - Slippers **
- Gay, lesbian and bisexual
  - Manic Mondays *
  - Slippers *
- Drivers
  - Workers **
- Construction/labour
  - Manic Mondays *
  - Slippers *
  - Workers **
- Hospitality
  - Manic Mondays *
  - Slippers *
  - Workers *
- Rural/regional
  - Manic Mondays *
  - Slippers *
  - Workers **
- Sex workers

- n/a

Note: * indicates less prevalence

** indicates greater prevalence.

For each target audience, if a sub group is not listed indicates little or no apparent representation of target audience in the behavioural sub group.

6.4 Dependent users

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For the purpose of this research dependent use has been categorised using the following definition: 'uncontrollable, compulsive drug seeking and use, even in the face of negative health and social consequences' [18]. This definition has been used as it encompasses both psychological as well as physical dependence. Both health and social problems are included as indicators of addiction, rather than symptoms related to physical withdrawal being used as the only determining factor.

Therefore, users in the dependent behavioural context have been determined based upon their claims of uncontrollable, compulsive cravings that cause them to use methamphetamines repeatedly. This can be a craving for either the drug, or the act of taking the drug (particularly injecting). Many within this behavioural context were motivated to use methamphetamines by the sense of 'normality' they believed the drugs provided, allowing them to 'get through the day'. Other motivations for use include the temporary escape that methamphetamine use provides from mental and lifestyle problems, and for many injectors, it is the psychological fulfilment gained from using the needle. The quotes below articulate these motivations.

> *"I just can't do much but stay in bed unless I have it".*
>
> *"The only time I feel normal and able to face the world is when I'm using".*
>
> *"It's an escape...I don't have to think about my life and myself".*
>
> *"It's all about the feel of the steel".*

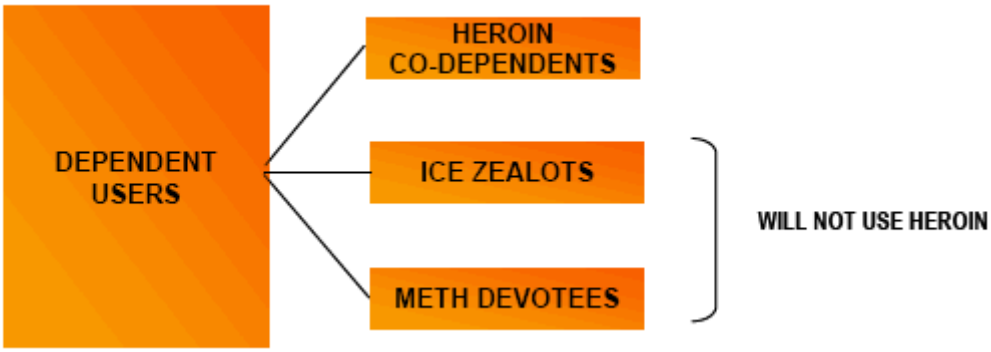
Use in this context is typically much 'heavier' than other user groups both in terms of frequency and dosage. Frequency of use among dependent users ranges from 3-4 days per week to several times per day. In regards to dosage, many claim to have built up a tolerance by this stage of drug taking and as a result are having more than one hit at a time to feel the effects[19]. In addition, the more pure forms of methamphetamines such as base or ice were used.

Dependents come from a broad cross-section of society. Some are from low socio-economic or unemployed backgrounds, while others work in skilled and semi-skilled employment, for example, clerical positions, nursing, IT, and finance. Although dependents are typically older than social users, usually aged 30 and above, some are as young as 25 years. The degree to which dependents appear to function within mainstream society tends to differ significantly according to both the primary drug used and the primary mode of administration.

Types of dependent users

Like other behavioural user groups, dependents also comprise a number of sub groups. Differences between these groups relate to demographic, poly drug behaviours, attitudes toward ice and mode of administration.

Figure 6: Dependent user sub groups



Text version of figure 6

This diagram shows dependent users split into three groups: heroin co-depentents, ice zealots and meth devotees. Ice zealots and meth devotees will not use heroin.

Meth devotees and ice zealots

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Meth Devotees and Ice Zealots are similar in some regards. Both groups crave the high achieved through methamphetamines, and dislike the idea of heroin. Both use it as a functional and social enabler.

> *"Why would you do slowey when you can use goey?"*

The majority of both sub groups include users who are in employment. As many place high importance on maintaining this foot hold in mainstream society, this often involves keeping their addiction confidential.

These sub groups also have some marked differences. 'Meth devotees' are typically older (aged 30 years or over) and cross the spectrum of occupations from skilled, unskilled to unemployed. They rarely use in a social context and their drug of preference is speed or base, although they will use ice if these are unavailable. Often they have been using methamphetamines for a extended period of time, and will often regard these drugs in the same way others regard their 'morning coffee' – as a necessary pick me up in the morning. The primary mode of administration is injection, although a minority snort. Meth Devotees are unlikely to be poly drug users.

In contrast, Ice Zealots are typically younger (aged 25-30 years), and are more likely to be unskilled, unemployed or part time workers. They use regularly in a social context, although this is more likely to be at house parties than going out to clubs or dance venues. The primary difference between these users and the 'Ice Preferrers' social user sub group, is that Ice Zealots use frequently alone throughout the week as they work flexible hours or not at all. Ice Zealots prefer the purity and intensity of ice to other methamphetamines, and their primary mode of administration is smoking. As they still use drugs regularly in social situations, they also regularly come into contact with and use other drugs such as speed, ecstasy and marijuana [20].

The impetus to dependency also differs between the two groups. For Ice Zealots, dependency appears to be more of a gradual slide from social smoking to more regular, solitary use. Some examples are provided the quotes below.

> *"It's something about the smoke, I just found myself wanting more and more. I'd put the pipe down and then 2 hours later I'd want it again. I'd wake up in the morning and want more".*

> *"My boyfriend and I used to do it together, and still do. But I'll also sneak it during the day now when he's at work and the baby's asleep."*

Meth Devotees, on the other hand, often relate their dependent use to a trauma or other instance in their life where they allowed their personal parameters on usage to slip. Examples included loss of a job, a relationship break up and being a victim of abuse. For one respondent, it was the dramatic increases he noticed in his productivity at that was the specific cause of his now

dependent use. Again, the quotes below contain examples.

> *"I use to only do it occasionally. One day I walked home to find my girlfriend in bed with my best friend and I couldn't deal with it, drugs were my escape. That was 10 years ago now."*

> *"I only ever used on a Friday night…I was a weekend only girl, until that bastard bashed the XXX out of me (partner of a number of years)".*

> *"I used at work a few times, realised no-one noticed, I got more done, so I just kept using."*

Heroin co-dependents

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Heroin Co-Dependents represent the extreme of all methamphetamine users. They typically use drugs on a daily basis, often several times a day. Drug use is frequently alone, but can also be with others who often have the same drug habits.

They are distinguishable from other dependent groups primarily by their current or past use of heroin. Those who were not currently using heroin were receiving heroin replacement treatment, such as methadone. Their principle mode of administering drugs is intravenously. While users from other dependent sub groups may also inject, Heroin Co-Dependents will often rationalise their motivation for using methamphetamines in this way as more for the psychological fulfilment of the needle, rather than the drug itself as is the case with Meth Devotees and Ice Zealots.

They may use methamphetamines for a number of reasons. The most common of which is the poor availability or quality of heroin, which is becoming an increasing problem for some. Second to this, is the preference to use methamphetamine while on methadone treatment as they are more likely to feel a 'hit' than if they used heroin. Lastly, some claim that methamphetamine helps to balance the docile effects of methadone:

> *"The methadone calms me down, the goey gets me going...I can still do things then while I'm on the methadone".*

Their preferred methamphetamines are base and ice, although usually Heroin Co-Dependents are the least discriminatory of all user groups in this regard.

Of all the user groups, Heroin Co-Dependents are perhaps the most homogenous. Similar to Meth Devotees, Heroin Co-Dependents are typically older than other user groups. They are typically the least functional of all the user groups, often unemployed and of low socio-economic status. Many also suffer a range of co-morbid physical and mental health issues. They are also more likely than other dependents to have a long history of contact with either drug treatment services or providers, such as needle and syringe programs and heroin replacement programs, or the criminal justice system. In many regards, Heroin Co-Dependents often appear to fit the widely held social stereotype of 'junkies'.

Summary of dependent user sub groups across target audiences

Table 8 summarises which of the target audiences are more prevalent in each of the three dependent user sub groups described above.

Table 8: Summary of dependent user sub groups across target audiences

Table 8 is presented as a list in this HTML version for accessibility reasons. It is presented as a table in the PDF version.

Summary of dependent user sub groups (ice zealots, meth devotees and heroin co-dependents) across target audiences:

- Young (18-24)
  - n/a
- Uni students

    - n/a
- Rave partiers
    - n/a
- General (25+)
    - Ice zealots **
    - Meth devotees **
    - Heroin co-dependents **
- Gay, lesbian and bisexual
    - n/a
- Drivers
    - Meth devotees *
- Construction/labour
    - Ice zealots *
    - Meth devotees *
- Hospitality
    - Ice zealots *
- Rural/regional
    - n/a
- Sex workers
    - Meth devotees *

Key: * indicate where target audiences also used in this context, but to a lesser extent.
** indicate the target audiences where usage was most prevalent.

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[17] The social experience of sharing the methamphetamine pipe is also commented on in McKetin, R., 2007, in *Illicit Drug Use in Australia: Epidemiology, use patterns and associated harm*, (2nd edition), Ross, J., (ed), National Drug & Alcohol Research Centre, 2007

[18] Leshner, Dr A.,Director of the National Institute of Drug Abuse within the US National Institute of Health, the essence of drug addiction on NIDA website

[19] Also stated in McKetin, R., 2007, in *Illicit Drug Use in Australia: Epidemiology, use patterns and associated harm*, (2nd edition), Ross, J., (ed), National Drug & Alcohol Research Centre, 2007

[20] McKetin, et al., 2005, cited in, in Illicit Drug Use in Australia: Epidemiology, use patterns and associated harm, (2nd edition), Ross, J., (ed), National Drug & Alcohol Research Centre, 2007, also identified this particular sub group in a discussion of who uses ice.

[21] Also found in McKetin et al., 2005, cited in *Illicit Drug Use in Australia: Epidemiology, use patterns and associated harm*, (2nd edition), Ross, J., (ed), National Drug & Alcohol Research Centre, 2007

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PUBLIC HEALTH

As Meth Use Surges, First Responders Struggle To Help Those In Crisis

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May 1, 2019 · 5:10 AM ET
Heard on Morning Edition

APRIL DEMBOSKY

FROM KQED

Kim has been living at the Epiphany Center, a treatment facility in San Francisco for women struggling with addiction, for the past six months. She says her teddy bear is her only material possession left from her past: "Because everything I had, I've lost over and over again."

April Dembosky/KQED

Amelia and her roommate had been awake for two days straight. They decided to spray-paint the bathroom hot pink. After that, they laid into building and rebuilding the pens for the nine pit bull puppies they were raising in their two-bedroom apartment.

Then the itching started. It felt like pinpricks under the skin of her hands. Amelia was convinced she had scabies, skin lice. She spent hours in front of the mirror checking her skin and picking at her face. She even got a health team to come test the apartment. All they found were a few dust mites.

"At first, with meth, I remember thinking, 'What's the big deal?' " says Amelia, who asked that we not reveal her last name to protect her family's privacy. "But when you look at how crazy things got, everything was so out of control. Clearly, it is a big deal."

While public health officials have focused on the opioid epidemic in recent years, another epidemic has been brewing quietly, but vigorously, behind the scenes. Methamphetamine use is surging in parts of the U.S., particularly the West, leaving first responders and addiction treatment providers struggling to handle a rising need.

Across the country, overdose deaths involving methamphetamine more

than quadrupled from 2011 to 2017. Admissions to treatment facilities for meth are up 17%. Hospitalizations related to meth jumped by about 245% from 2008 to 2015. And throughout the West and Midwest, 70% of local law enforcement agencies say meth is their biggest drug threat.

But policymakers in Washington, D.C., haven't kept up, continuing to direct the bulk of funding and attention to opioids, says Steve Shoptaw, an addiction psychologist at UCLA in Los Angeles, where he hears one story after another about meth destroying people's lives.

"But when you're in D.C., where people are making decisions about how to deploy resources, those stories are very much muffled by the much louder story about the opioid epidemic," he says.

The stimulant drug methamphetamine is a white, bitter-tasting crystalline powder that dissolves in water or alcohol

and is snorted, injected or smoked.

Getty Images/Science Source

Even within drug treatment circles, where you'd think everyone would be on the same side, there's a divide. Opioid addiction advocates are afraid their efforts to gain acceptance for measures like needle exchange programs and safe injection sites will be threatened if meth advocates demand too much.

"The bottom line is, as Americans, we have just so much tolerance to deal with addiction," Shoptaw says. "And if the opioid users have taken that tolerance then there's no more."

So local lawmakers in San Francisco are trying to get a grip on the toll meth is taking on their city's public health system on their own. Mayor London Breed recently established a task force to combat the epidemic.

"It's something we really have to interrupt," says San Francisco District 8 Supervisor Rafael Mandelman, who will co-chair the task force. "Over time, this does lasting damage to people's brains. If they do not have an underlying medical condition at the start, by the end, they will."

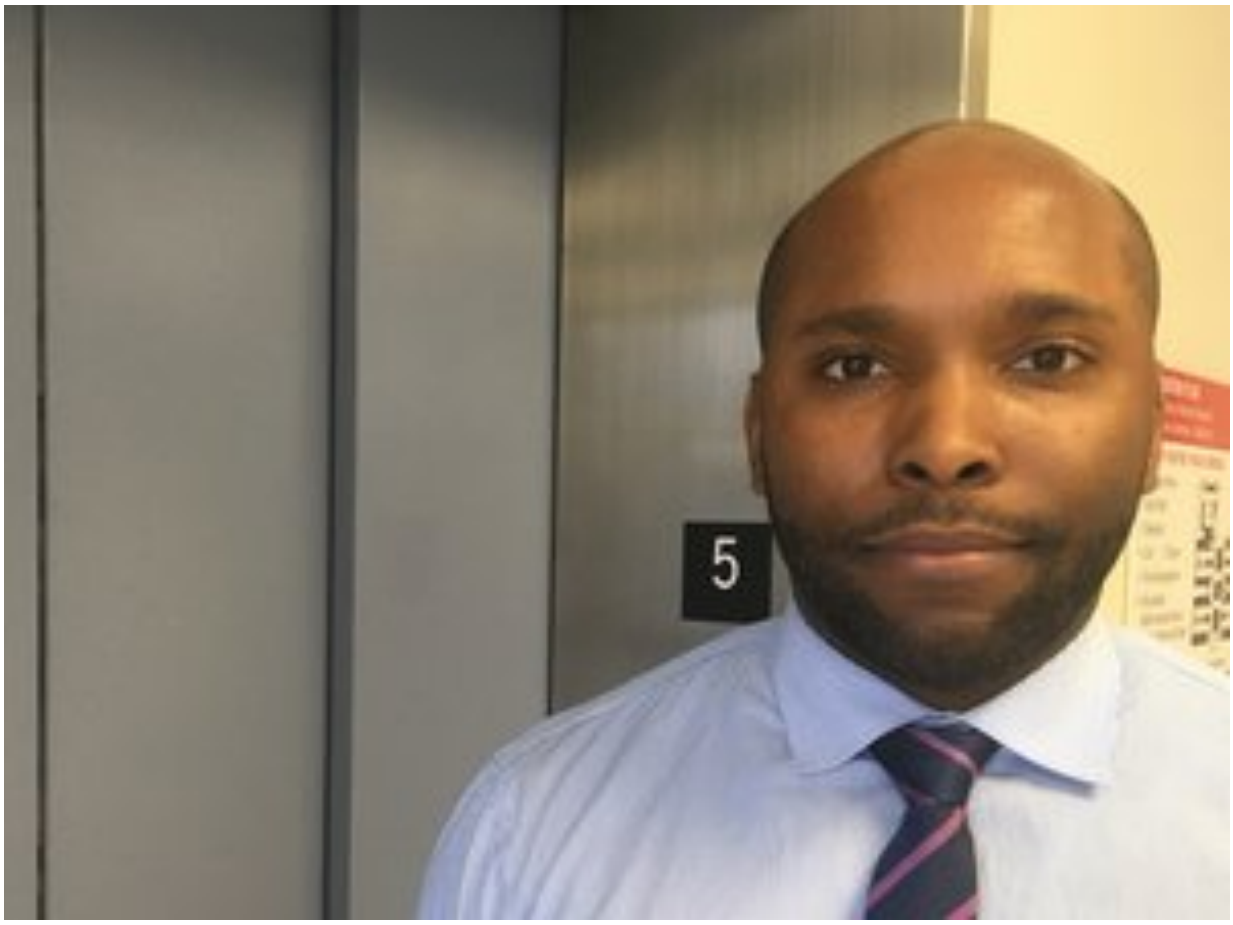
Since 2011, emergency room visits related to meth in San Francisco have jumped 600% to 1,965 visits in 2016, the last year for which ER data is available. Admissions to the hospital are up 400% to 193. And at San Francisco General Hospital, of 7,000 annual psychiatric emergency visits last year, 47% were people who were not necessarily mentally ill — they were high on meth.

"They can look so similar to someone that's experiencing chronic schizophrenia," says Dr. Anton Nigusse Bland, medical director of psychiatric emergency services at Zuckerberg San Francisco General

Hospital. "It's almost indistinguishable in that moment."

Someone who has methamphetamine-induced psychosis, he says, "they're often paranoid, they're thinking someone might be trying to harm them. Their perceptions are all off."

For example, someone starts walking into traffic on Sixth Street while shouting and taking off his shirt. A bystander calls 911 and reports a mentally disturbed person, and then the police come and deliver him to Nigusse Bland's department.



Dr. Anton Nigusse Bland, head of psychiatric emergency services at Zuckerberg San Francisco General Hospital.
April Dembosky/KQED

If the person is really agitated, doctors might administer a

benzodiazepine to calm down, or even an anti-psychotic. Otherwise, the treatment is just waiting 12 to 16 hours for the meth to wear off. No more psychosis.

"Their thoughts are more organized, they're able to maintain adequate clothing. They're eating, they're communicating," Nigusse Bland says. "The improvement in the person is rather dramatic because it happens so quickly."

Trends in drug use come in waves

For some people recovering from addiction, the memories of meth-induced psychosis are part of what motivates them to stay sober.

For Amelia, the scabies scare is what alerted her mother to her addiction, forcing an intervention. Even though she did not have scabies, the itchy feeling and the fear are vivid, even a year and a half later.

"I still don't really want to say it out loud that it wasn't real," says Amelia, now 33.

For Kim, another woman in recovery, there was one day last year when she says she went wine tasting with a friend in Sonoma. She was high on Xanax and speed.

"I was crazy," says Kim, 47, who also asked that we not reveal her last name. "Meth causes people to act completely insane."

She and her friend got in an argument in the car. Kim thought someone was behind them, following them. She was utterly convinced. And she had to get away.

"I jumped out of the car and started running, and I literally ran a mile. I

went through water, went up a tree, and I was literally running for my life," she says. "I literally thought I was being chased."

Kim was soaking wet when she walked into a woman's house, woke her from bed and asked for help. When the woman went to call the police, Kim left and found another woman's empty guest house to sleep in. Kim says she just wanted to get warm.

"But then I woke up and stole her car," she says.

That's how Kim ended up in jail, in a residential treatment program in San Francisco, part of the steady rise in people seeking help for meth addiction. Rehab admissions in San Francisco for meth are up 25% since 2015.

The trend in rising stimulant use is nationwide: cocaine on the East Coast, meth on the West Coast, says Dr. Daniel Ciccarone, a professor of medicine and substance use researcher at the University of California, San Francisco.

"It is an epidemic wave that's coming, that's already here," he says. "But it hasn't fully reached our public consciousness."

Drug preferences are generational, Ciccarone says. They change with the hairstyles and clothing choices, like bell bottoms or leg warmers. It was heroin in the 1970s, cocaine and crack in the '80s. Then opiate pills. Then methamphetamine. Then heroin. And now meth again.

"The culture creates this notion of let's go up, let's not go down," Ciccarone says. "New people coming into drug use are saying, 'Whoa, I don't really want to do that. I hear it's deadly; people look really doped up and they're not that fun to be with. I'm going in a different direction.'

"

Kim has been with meth through two waves. When she got into speed in the 1990s, she was hanging out with a lot of bikers, going to clubs in San Francisco.

"Now what I see, in any neighborhood, you can find it. It's not the same as it used to be where it was kind of taboo," Kim says. "It's more socially accepted now."

Dying from meth

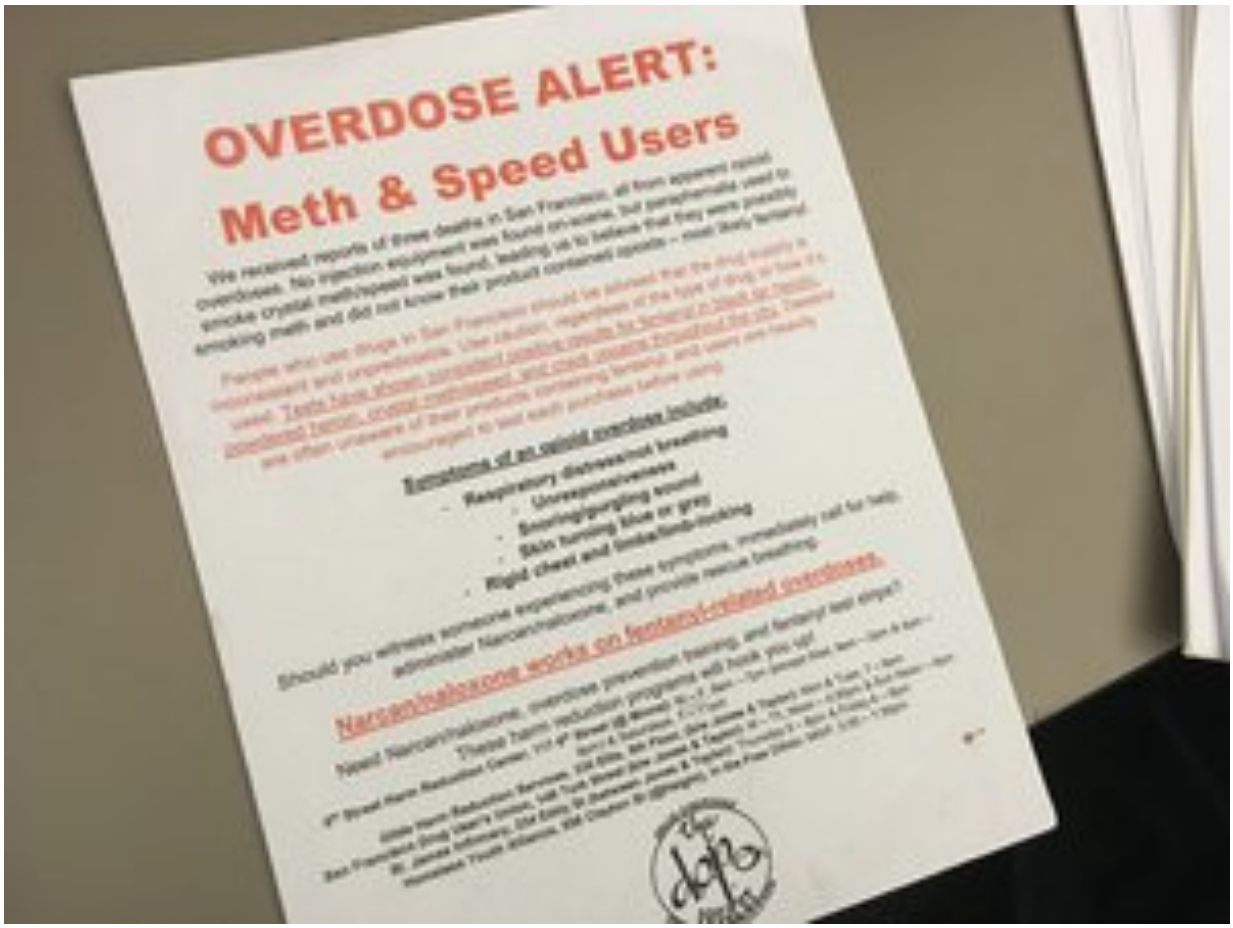
A hint about who is using meth today comes from the data on deaths. Meth is not as lethal as opioids: 47,600 people died of opioid-related overdoses in 2017 compared to 10,333 deaths involving meth. (About half of those involved a mix of meth and opioids.) But the death rate for meth has been rising. Meth-related deaths in San Francisco doubled since 2011 and more than quadrupled nationally. This is another indication that more people are using meth and that today's supply is very potent, says UCSF's Ciccarone.

Another hypothesis that experts have come up with to explain the growth in meth-related overdoses is that meth users are aging. Most meth deaths are from brain hemorrhage or a heart attack, which would be unusual for a 20-year-old.

"Because your tissue is so healthy at that age," says Phillip Coffin, a physician and the director of substance use research at the San Francisco Department of Public Health. "Whereas when you're 55 years old and using methamphetamine, you might be at higher risk for bursting a vessel and bleeding and dying from that."

Older adults have higher blood pressure, maybe heart disease, that makes their heart weaker.

"So stimulant-related death, really, you shouldn't see it affect so many young people," Coffin says.



A meth overdose alert from the Drug Overdose Prevention and Education Project.

April Dembosky/KQED

The San Francisco AIDS Foundation runs a 12-week program called Positive Reinforcement Opportunity Project to help men who have sex with men stop using meth. The project's program manager, Rick Andrews, has noticed a trend in older men coming in for help.

"Older gentlemen who grew up in the time of HIV and AIDS initially,

maybe they led very safe lifestyles, and now they're older," he says.

Now that things are different with HIV — there's treatment, there's a prevention pill, PrEP — they're taking a new approach to the often drug-fueled party scene.

"They feel like they've missed out and they want to have a little fun and make up for lost time maybe," Andrews says.

Rick Andrews (right) runs a drug counseling and testing program at the San Francisco AIDS Foundation to help men get their meth use under control.

Courtesy of the San Francisco AIDS Foundation

Another explanation for the rising death rate is that meth is contaminated. And that affects everyone, old and young. Last year, three

young people in San Francisco died after smoking meth together. It turns out the meth had fentanyl in it. The synthetic opioid has been causing waves of heroin overdoses across the country, but now it's showing up mixed into cocaine and meth.

Most researchers believe the contamination is accidental.

"The whole idea of the evil drug pusher who's trying to create a market by getting their cocaine users hooked on fentanyl — I would highly doubt that," says UCSF's Ciccarone.

Dealers know that people are particular about their drugs, he says. It doesn't make sense to alienate a customer base like that. He compares it to coffee drinkers' preference for a favorite style of coffee.

"Folks that are doing hardcore illicit drugs can be pretty fussy, too," he says. "And most meth users really, really, really, really don't want an unbeknownst fentanyl put into their methamphetamine."

More likely, Ciccarone says, the same table that was used to cut and bag fentanyl later got used to bag meth.

Deliberate or not, health officials call this poisoning. They started distributing fentanyl test strips to meth users so they can test their drugs. But counselors like Rick Andrews say the strips aren't refined — even trace amounts will give a positive result.

"I hear guys saying, 'Oh, there's test strips and I'm testing. It's positive, but I do it anyway and everything's fine,' " Andrews says.

That's why they're also giving out Narcan, the nasal spray that can reverse an opioid overdose, Andrews says. They're telling meth users to carry it just in case.

Recovery

Over her two decades of meth use, Kim has been through drug treatment more than a dozen times. Relapse is part of recovery, and among meth users, 60% will start using again within a year of finishing treatment. Unlike opioids, there are no medication treatments for meth addiction, which makes it particularly hard to treat.

Kim finished her last round of treatment in April at a six-month residential program for women in San Francisco called The Epiphany Center. She came to Epiphany directly from jail, after serving time for her housewarming spree and stealing the car. She says in the first 30 days, all she could do was try to clear the chaos from her mind.

"You have to get used to sitting with yourself, which is essential for life, is to get along with your own self," she says.

Kim is hopeful that this recent treatment will stick. She's living in transitional housing now, she has a job, and she has been accepted to a program at the University of California, Berkeley to finish her college degree.

"I've gone through 12 different programs and it's been for my children, for my mom, for the courts. I've never come to be there for myself," Kim says. "So it's like I've come to a place where it has to be for me."

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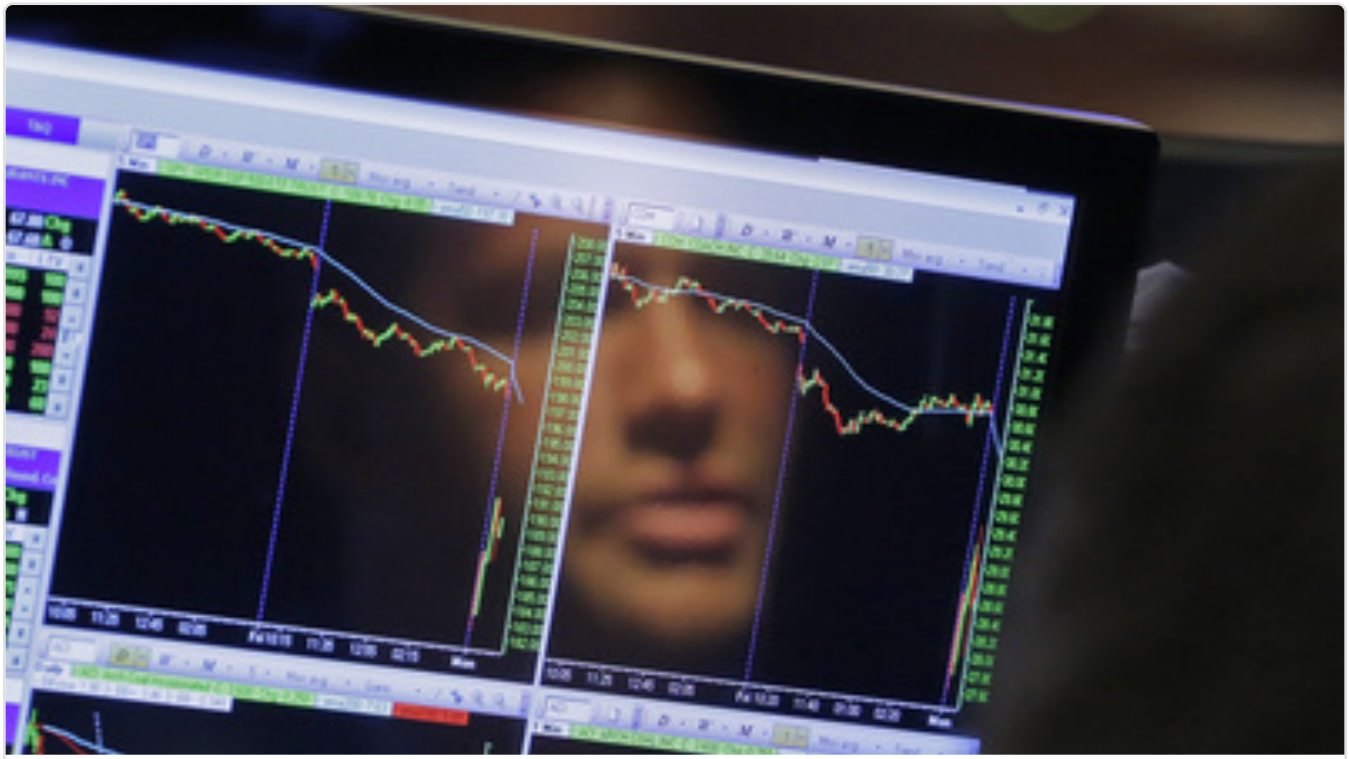

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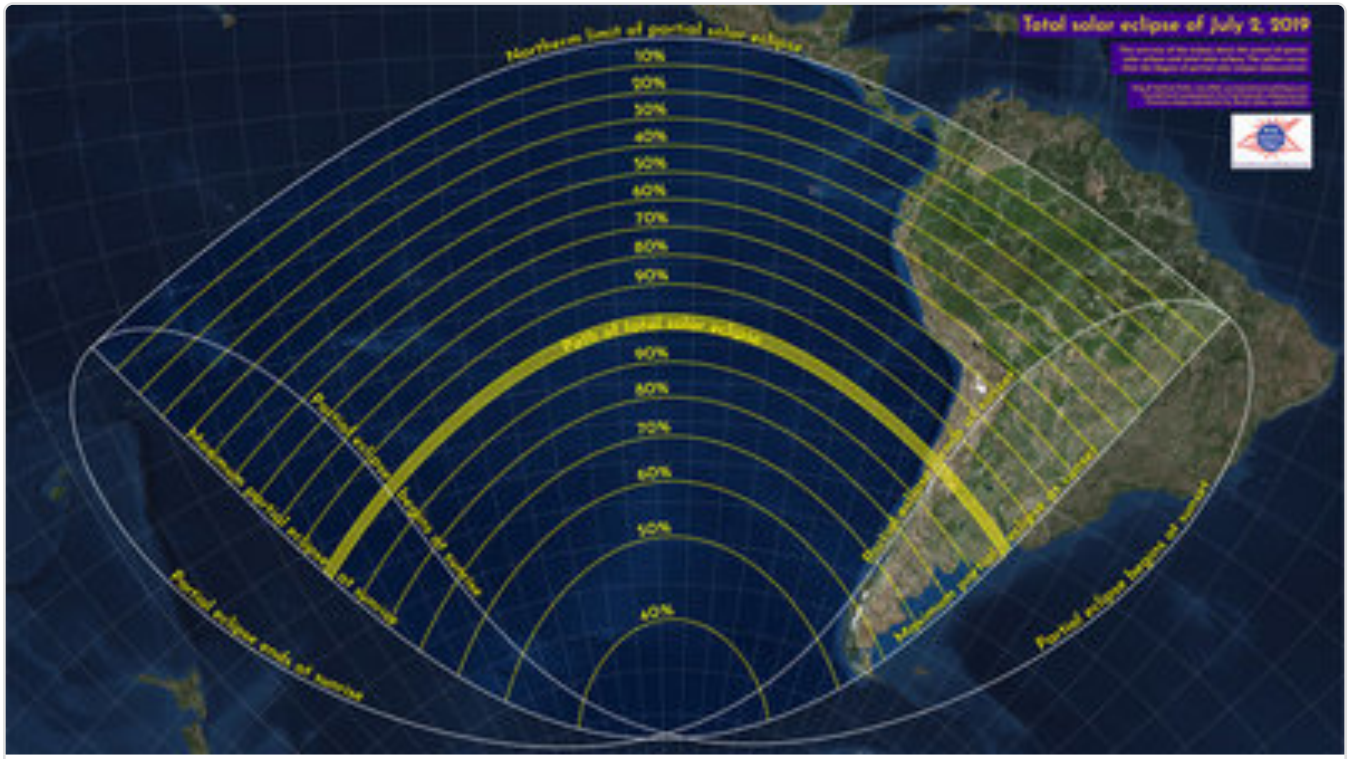

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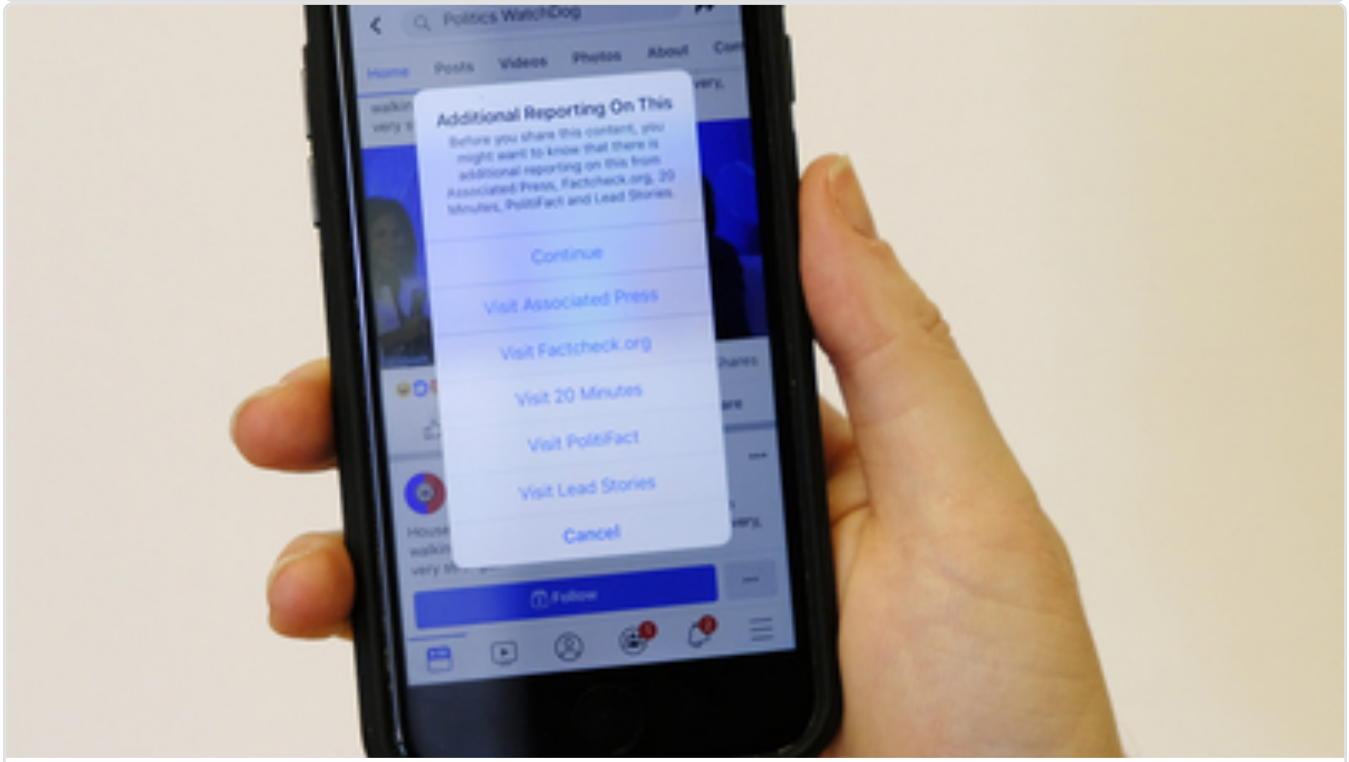

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Emerging research on methamphetamine

Jane Carlisle Maxwell

Purpose of review

To describe and review the literature published on methamphetamine in 2003–2004, with a particular focus on patterns of use, its effects on the user and society, and progress being made towards effective treatment strategies.

Recent findings

The methamphetamine epidemic continues to grow, dominating drug use trends in many parts of the world, and signifying an increasing need for effective treatment. In addition to the already-documented physical effects of the drug, preliminary evidence suggests methamphetamine dependence may cause long-term neuronal damage. Recently abstinent users have been found to do poorly on neurocognitive tests of attention and motor skills, both factors that can adversely affect treatment outcomes. Methamphetamine use is also implicated in aggression and violence and there are increasing presentations to emergency rooms. It also affects the developing fetus, as well as children and adults who are exposed to toxic chemicals at laboratory sites. Outpatient programs, such as the Matrix Model, show improved in-treatment performance. Case management was found to be an effective intervention. Agonist-type pharmacotherapy in combination with quality behavioral therapy should produce benefit and a reduction in risks caused by stimulant abuse.

Summary

The increasing evidence that methamphetamine has adverse effects on the human brain indicates the pressing need for effective prevention and treatment approaches. There is a need to take these findings, particularly those that involve cognitive deficits, into consideration in current treatment programs and when developing new treatments.

Keywords

amphetamine, amphetamine-type substances, Ice, methamphetamine, methamphetamine treatment, speed

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Abbreviations

ATS amphetamine-type stimulant
MRI magnetic resonance imaging

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Introduction

The use of methamphetamine and other amphetamine-type stimulants (ATSs) has become an epidemic in many parts of the world. This article examines the research published during 2003–2004 and covers not only the effects on users, but also the impact on other members of society. As the different terms used in the articles reviewed in this paper show, one of the problems in monitoring use is that distinctions between the different types of amphetamine and methamphetamine are not always made and the terms are often used interchangeably.

Prevalence and patterns of use

Amphetamine-type substances come in different forms and with different names. 'Speed' ('meth', 'crank') is a powdered methamphetamine of relatively low purity and sold in grams or ounces. It can be snorted or injected. 'Pills' can be pharmaceutical grade stimulants such as dexamphetamine, or they can be methamphetamine powder that has been pressed into tablets and sold as amphetamines or Ecstasy. Pills can be taken orally, crushed for inhalation, or dissolved in water for injection. There is also a damp, sticky powder of higher purity that is known as 'Base' in Australia [1]. 'Ice', also known as 'Crystal', is methamphetamine that has been 'washed' in a solvent to remove impurities; it has longer-lasting physical effects and purity levels above 80% [2]. Ice can be smoked in a glass pipe, 'chased' on aluminum foil, mixed with marijuana and smoked through a bong, or injected.

The main source countries for methamphetamine are Myanmar, China, and the Philippines [3]. Methamphetamine is also produced in Mexico and California in 'Super Labs' which can make 10 or more pounds per 24 h using diverted ephedrine or pseudoephedrine, and it is also made in small laboratories ('box labs') by independent 'cooks' who use cold and influenza medications.

The United Nations Office on Drugs and Crime [3] estimates that 30 million people use ATSs compared

with 15 million who use opiates and 13 million who use cocaine. Sixty percent of ATS users (mostly methamphetamine users) live in Asia. The annual prevalence of use among those aged 15–64 was found to be highest in Thailand (5.6% in 2001), Australia (4.0% in 2001), New Zealand (3.4% in 2001), the Philippines (2.8% in 2000), Honduras (2.5% in 1997), the UK (1.6% in 2003), the US (1.4% in 2002), Taiwan (1.2% in 2001), the Czech Republic (1.1% in 2002), South Africa and Germany (0.6% in 2002), and Japan (0.3% in 2001) [4].

Caulkins [5••] has assessed the US methamphetamine epidemics to be more complex than other drug epidemics such as cocaine or Ecstasy because of the extreme spatial variation in patterns of use. Use has stabilized at endemic levels in the West while it is still a growing epidemic in the Midwest and is just beginning in the East. Caulkins has made the following predictions: methamphetamine use will grow very quickly for a number of years in specific cities; use may reach high levels; a substantial proportion of the nation's population lives in regions where methamphetamine is not yet widely available; and the drug is spreading into regions that previously had little methamphetamine use.

The increase in the supply and consumption of ATSs in Southeast Asia has implications for neighboring countries such as Australia because of the geographic proximity and the potential 'spillover' of the market into Australia [6•]. The 2003 Party Drug survey found that Ice users (compared with users of Speed or Base) were significantly more likely to report that they had 'binged' on stimulants in the past 6 months (i.e. used the drug continuously for more than 48 h without sleep) and to report that drug use caused social, work, and financial problems [7]. A study of a sample of 'crystal meth' users in Sydney found that users reported benefits that included alertness, energy, aphrodisiac effects, sociability, euphoria, and loss of inhibitions. Although most had not had extensive experience with Ice, they reported high rates of physical and psychological side effects, including 'comedown', paranoia, inability to sleep, addiction, and aggression [8•].

Risk of HIV

Many methamphetamine users are at high risk of sexually transmitted and blood-borne diseases. A study of 139 HIV-negative heterosexuals who had become dependent on methamphetamine found that they used the drug to get high, to get more energy, and to party. They reused syringes, shared needles, drank alcohol daily, used other drugs, had unprotected sex, had multiple sex partners, and engaged in marathon sex [9•]. Use of methamphetamine, and particularly Ice, has increased at gay circuit and dance parties. Ice appears to be especially sexually arousing and disinhibitory and is strongly associated with sexual behaviors that put men at risk from HIV infection [10•]. Sex and the use of methamphetamine are not only integrally connected, but participants report sex on methamphetamine as 'compulsive' and 'obsessive', with loss of control over their sexual expression [11•]. A study of 194 HIV-positive men who had sex with men found that methamphetamine injectors not only had more years of use and were heavier users, but they scored significantly higher on measures of impulsivity and experiences of rejection and lower on measures of emotional support [12•]. Medical complications for methamphetamine abuse in HIV-infected patients include hypertension, hyperthermia, rhabdoymyolysis, and stroke, and some researchers suggest that dopaminergic systems are vulnerable to the combined neurotoxity of HIV infection and methamphetamine [13•].

Use in the workplace

There is evidence that some individuals may use methamphetamine in the work arena. A report dated *22* July 2004 from Quest Diagnostics [14], which provides workplace drug testing, found that among general US workforce employees, the incidence of positive drug tests attributed to amphetamines rose from 0.34% in 2002 to 0.49% in 2003 – a 44% increase, which is the largest single-year increase in amphetamine use documented by the Drug Testing Index over the past 5 years.

Impact of methamphetamine on others

In a trauma center serving Hawaii, patients who were positive for amphetamine or methamphetamine were more likely to have intentional self-inflicted injury or intentional assaults. They were older, had significantly longer hospital stays, significantly higher hospital charges, and were more likely to be admitted to hospital. Methamphetamine use results in trauma center resource utilization out of proportion to injury severity [15].

Methamphetamine also places a burden on emergency departments in terms of the treatment of patients who suffer burns in methamphetamine laboratory explosions. These burns patients were found to require two to three times the standard Parkland formula resuscitation, and burns larger than 40% of the total body area resulted in 100% mortality [16]. Patients admitted to a burns unit also present new challenges for the treating team because such patients can become violent and frequently need assistance with detoxification. Routine drug screens are mandatory in identifying methamphetamine users to alert burns unit personnel to particular management problems and to target individuals who may be receptive to drug rehabilitation [17]. In addition, secondary contamination injuries to emergency department personnel result when exposed victims (including those injured as methamphetamine is being manufactured) enter the department without being properly decontaminated [18].

Methamphetamine use during pregnancy may affect the developing fetus. Methamphetamine exposure throughout gestation has been associated with decreased growth in infants exposed only for the first two trimesters. They were found to be significantly smaller for gestational age compared with the unexposed group; 4% required pharmacologic intervention for withdrawal from methamphetamine. Methamphetamine-exposed infants whose mothers smoked tobacco had significantly decreased growth relative to infants exposed to methamphetamine alone [19•]. Animal studies have found a range of physical, motor, neurotransmitter, and behavioral effects in methamphetamine-exposed rats and their offspring, including increased maternal and offspring mortality, retinal defects, cleft palate and rib malformations, decreased rate of physical growth, and delayed motor development.

Neurotoxic effects include neurochemical alterations in areas of the brain associated with learning, leading to cognitive impairment, behavioral deficits, increased motor activity, and enhanced conditioned avoidance responses. Human studies are limited, but the findings suggest that children may be at risk developmentally due to both the direct effects of prenatal drug exposure and the caregiving environment associated with that drug use. Maternal drug use is associated with risk factors such as poverty, chaotic and dangerous lifestyles, symptoms of psychopathology, history of childhood sexual abuse, and involvement in difficult or abusive relationships with male partners [20•].

Children are frequently found in laboratory surroundings and are exposed to toxic chemicals and fumes through absorption, inhalation, or ingestion, as well as being in homes with poor sanitation, hygiene, and nutrition. There can also be a high incidence of developmental delays. The California drug-endangered children's units were created to address the needs of these children though collaborative efforts among child protective workers, district attorneys, physicians, and police officers [21•].

Effects of methamphetamine on users

Methamphetamine use in the short term causes increases in heart rate, blood pressure, temperature and rate of breathing, constriction of blood vessels, and cardiac arrhythmia. Over longer periods of time, methamphetamine use is associated with health problems such as stroke, cardiac valve sclerosis, decreases in lung function, pulmonary hypertension, poorer cognitive functioning, and poorer mental health. Current health problems among methamphetamine users were predicted by greater age and by more prolonged methamphetamine use, especially among younger people. Reduction of methamphetamine use among younger people is important in promoting their later health. Drug treatment services could be improved by a greater understanding of how early experiences influence health later [22••].

Methamphetamine induces dose-dependent brain hyperthermia that precedes and is greater than overall body hyperthermia, suggesting methamphetamine-induced neuronal activation is a contributing source of that hyperthermia. Methamphetamine administered during social interaction was found to produce stronger and longer-lasting increases in brain and body temperature than those induced by the drug alone, heating the brain in some animals near its biological limit, which increases the risk for adverse effects [23•].

In Thailand, a high frequency of recent amphetamine use has been found among hospital patients with malaria. Oral use of amphetamines may lead to misdiagnosis, since coma and fever are features of amphetamine poisoning as well as malaria. The excessive sleepiness after withdrawal from amphetamines can prompt concerns that the patient is developing cerebral malaria or hypoglycemia. Amphetamines interact with drugs such as catecholamines, which are used in antimalarial treatment [24].

Patients taking amphetamines are also at increased risk of gingival enlargement [25], as well as chewing and grinding movements (bruxism) [26].

Methamphetamine abuse adversely impacts social support and social networks, as well as behavioral functioning [27]. It produces a variety of effects including irritability, physical aggression, hyperawareness, hypervigilance, and psychomotor agitation. Chronic intoxication can produce a psychotic paranoid state with frightening delusions that may result in aggressive acts. With increased dosage and duration of administration, amphetamines can produce delirium, which is manifested by disorientation, confusion, fear, and anxiety. During high-dose use, individuals can experience stimulant-induced psychosis characterized by delusions, paranoid thinking, and compulsive behavior. There is also substantial evidence that the effects caused by amphetamines are associated with violence [28•].

The Methamphetamine Treatment Project in California found participants had high levels of psychiatric symptoms, particularly depression and attempted suicide, as well as anxiety and psychotic symptoms. They reported high levels of problems controlling anger and violent behavior, with a correspondingly high frequency of assault and weapons charges. The findings support the value of integrated treatment for co-occurring conditions, especially the importance of training counseling staff to handle psychotic symptoms when needed [29•]. This project also found that 80% of women and 26% of men

reported abuse or violence from their partner. Men were more likely to report experiencing violence from friends and others. Past and current interpersonal violence is a characteristic of the lifestyles of the majority entering treatment for methamphetamine dependence [30•].

Methamphetamine use has been related to myocardial infarction, pulmonary edema, and aortic dissection. Acute coronary syndrome is common in patients hospitalized for chest pain after methamphetamine use and the frequency of other potentially life-threatening cardiac complications is appreciable. While a normal electrocardiogram lowers the likelihood of acute coronary syndrome, an abnormal finding is not helpful in distinguishing patients with or without the condition. These events occur in patients with and without underlying coronary disease and may involve multiple pathophysiologic mechanisms [31•]. Wijetunga *et al.* [32•] described cardiomyopathy due to methamphetamine exposure, finding that the pathogenesis is probably similar to that of cocaine and catecholamine-induced cardiomyopathy.

Persecutory delusion was the most common lifetime psychotic symptom, followed by auditory hallucinations, strange or unusual beliefs, and thought reading among methamphetamine psychotic inpatients in a multicountry study involving Australia, Japan, the Philippines, and Thailand. Auditory hallucinations were the most common current symptom, followed by strange or unusual beliefs and visual hallucinations. Apart from a factor of anxiety and depression, the results yielded a two-factor model of psychotic symptoms. The negative syndrome comprised impaired speech, psychomotor retardation, and flattened/incongruous affects. The positive syndrome consisted of delusions, hallucinations, and incoherent speech. Both positive/disorganized and negative syndromes should be taken into account in assessing methamphetamine psychotic symptoms [33•].

A study of 405 methamphetamine users in Taipei found pre-morbid schizoid/schizotypical personality predisposed methamphetamine users to develop psychoses. The greater the vulnerability, the longer the psychosis would persist. Those with psychosis were younger at first use, used larger amounts, had significantly higher mean Premorbid Schizoid and Schizotypal Trait scores, and higher rates of depressive disorder, alcohol dependence, and antisocial personality disorders [34•].

A prospective study of the methamphetamine withdrawal syndrome found moderate levels of depression during the first several days of abstinence, with minimal levels thereafter. The most prominent symptoms were anhedonia, irritability, and poor concentration. The withdrawal syndrome associated with methamphetamine dependence varied considerably in intensity and duration, but generally was mild and resolved quickly for most individuals. Retrospective studies had reported a more prolonged time course [35•]. Methamphetamine-dependent individuals who were abstinent for 5–14 days performed significantly worse than controls on neurocognitive measures sensitive to attention/psychomotor speed, on measures of verbal learning and memory, and on executive system measures sensitive to fluency. These individuals were more likely than nondrug users to be classified as impaired in the areas of attention/psychomotor speed, learning and memory, and executive systems functioning. The differences were not attributable to demographic profile, estimated premorbid IQ, and level of self-reported depression. The severity of neurocognitive impairment is likely associated with worse functional outcomes, including poorer vocational functioning and an elevated risk of relapse to dependence [36••]. Recently, abstinent methamphetamine-dependent patients demonstrated quantitative EEG abnormalities that are consistent with a generalized encephalopathy. These changes in brain electrical activity are frequently associated with a range of cognitive and psychiatric abnormalities [37•].

When the cognitive performance of those who remained abstinent, relapsed, or continued to use during treatment was compared, the performance of the relapse group was worse than the abstinent group for episodic memory and significantly worse than that of the group that continued to use during treatment. This suggests that treatment providers can expect the cognitive problems of methamphetamine users entering treatment to worsen, at least during the first 3 months of abstinence, and that these users might benefit from the inclusion of strategies to compensate for cognitive problems. The specific impairment associated with episodic, but not working, memory found for the relapse group suggests that a mechanism may exist that underlies both recall and recognition and that this mechanism may be particularly vulnerable to the effects of relapse to methamphetamine use [38•].

Among 50 twin pairs in which only one member had heavy stimulant abuse (cocaine/amphetamines), abusers performed significantly worse than nonabusers on functions of attention and motor skills. Abusers, however, performed significantly better on one test of attention that measured visual vigilance. Within the abuser group, higher levels of stimulant use were largely uncorrelated with neuropsychological test scores, although a few significant correlations indicated better functioning with more stimulant use. The study demonstrated that deficits in attention and in motor skills persisted after 1 year of abstinence from stimulant use and raised hypotheses regarding relative strengths on a vigilance task among abusers [39•].

Preliminary evidence from the literature on neuropsychological effects of methamphetamine use on neurotransmitters and cognition suggests that methamphetamine dependence may cause long-term neuronal damage in humans, with concomitant deleterious effects on cognitive processes such as memory and attention [40••]. Abusers of methamphetamine have higher self-ratings of depression and anxiety than controls and they differ significantly in relative regional glucose metabolism: lower in the anterior cingulate and insula and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum. The relationships between relative glucose metabolism in limbic and paralimbic regions and self-reports of depression and anxiety in methamphetamine abusers suggest that these regions are involved in affective dysregulation and may be an important target for therapeutic intervention during early abstinence and withdrawal when mood disturbances may complicate treatment [41••].

Methamphetamine abusers who remain abstinent for 9 months or longer show modest improvement in performance on some tests of motor skill and memory and they appear to recover from some of the drug's damaging effects on metabolism in the thalamus. However, drug-related deficits appear to persist longer in the striatum. Persistent decreases in striatal metabolism in methamphetamine abusers could reflect long-lasting changes in dopamine cell activity and decreases in the nucleus accumbens could account for the persistence of amotivation and anhedonia in detoxified methamphetamine abusers. The recovery of thalamic metabolism could reflect adaptation responses to compensate for the dopamine deficits, and the associated improvement in neuropsychological performance further indicates its functional significance [42•].

Methamphetamine damages monoaminergic systems in the mammalian brain. Recent reports have provided conclusive evidence that methamphetamine can cause neuropathological changes in the rodent brain via apoptotic mechanisms akin to those reported in various models of neuronal death. In addition, the deleterious effects of the drug consist of cell death in the cortex, striatum, and hippocampus [43••]. Using magnetic resonance imaging (MRI) and new computational brain mapping techniques, Thompson *et al.* [44••] demonstrated systematic brain structural deficits with chronic methamphetamine abuse in humans and related these deficits to cognitive impairment. MRI-based maps suggest that chronic methamphetamine abuse causes a selective pattern of cerebral deterioration that contributes to impaired memory performance. Methamphetamine may also selectively damage the medial temporal lobe and, consistent with metabolic studies, the cingulate-limbic cortex, inducing neuroadaptation, neuropil reduction, or cell death. Prominent white matter hypertrophy may result from altered myelination and adaptive glial changes, including gliosis secondary to neuronal damage. These brain changes may help account for the symptoms of methamphetamine abuse, providing therapeutic targets for drug-induced brain injury.

While substantial inroads have been made toward understanding the neurobiology of amphetamine-induced toxicity, the mechanisms by which amphetamines lead to selective dopamine and 5-HT damage are not yet known, nor are the mechanisms, time course, and features of recovery. A focused effort toward defining the functional consequences of amphetamine toxicity in animals and humans is in order and is likely to yield important information regarding the basic neurobiology of monoaminergic neurons, their involvement in neurodegenerative diseases and their role in normal and abnormal behavior [45•].

Treatment

Treatment for methamphetamine abuse is a recent phenomenon and, for the most part, is based on previous treatment approaches for cocaine abuse [27]. But there are some aspects of methamphetamine-related disorders that are specific to the consequences of using the drug. The development of treatments is particularly critical for a number of user groups including those who experience persistent psychosis, pregnant women and women with children, gay and bisexual men, and users involved in the criminal justice system [46••], as well as for rural populations and Hispanics.

A randomized controlled trial of methamphetamine-dependent gay and bisexual males found that drug treatment produced significant reductions in methamphetamine use and sexual risk behaviors. Drug treatment merits consideration as a primary HIV prevention strategy for this population [47•] as it resulted in reduced sexual risk behaviors and reduced stimulant use after treatment [11•].

Volkow *et al.* [48••] proposed a model to explain the loss of control and compulsive drug intake that characterize addiction. In drug addiction, the value of the drug and drug-related stimuli is enhanced at the expense of other reinforcers. This is a consequence of conditioned learning and of the resetting of reward thresholds as an adaptation to the high levels of stimulation induced by drugs of abuse. During exposure to the drug or drug-related cues, the memory of the expected reward results in overactivation of the reward and motivation circuits while decreasing the activity in the cognitive control circuit. This contributes to an inability to inhibit the drive to seek and consume the drug and results in compulsive drug intake. Treatment strategies can

include (a) interventions to decrease the rewarding value of drugs, such as pharmacological treatments that interfere with the drug's reinforcing effects, as well as treatments that make the effects unpleasant; (b) interventions to increase the value of the nondrug reinforcers, such as pharmacological and behavioral treatments that increase sensitivity to natural reinforcers and establish alternative reinforcing behaviors; (c) interventions to weaken learned drug responses, such as behavioral treatments to extinguish the learned positive associations with the drug and drug cues but also treatments that promote differential reinforcement of other behaviors; and (d) interventions to strengthen frontal control, such as cognitive therapy. This model highlights the need for therapeutic approaches that include pharmacological as well as behavioral interventions in the treatment of drug addiction.

Psychosocial and behavioral approaches are currently the primary treatments for methamphetamine-dependent individuals, although research continues on replacement pharmacotherapies. The Center for Substance Abuse Treatment's Tip #33: Treatment of stimulant abuse [49] remains a basic guide for clinicians. The Matrix Model, a manualized 16-week outpatient treatment approach for treating stimulant disorders, combines techniques and materials from the cognitive behavioral therapy literature to include accurate information on the effects of stimulants, family education, Twelve-Step program participation, and positive reinforcement for behavior change and treatment compliance. It has been assessed in several large groups and outcomes have demonstrated that, in general, the treatment response of methamphetamine-dependent individuals was positive. Compared with clients who participated in outpatient 'treatment as usual', Matrix clients were 38% more likely to stay in treatment, 27% more likely to complete treatment, and 31% more likely to have negative methamphetamine urine test results. However, the Matrix approach did not produce superior outcome at discharge or follow-up, although, with its multiple components in an intensive structured protocol, it significantly improved in-treatment performance which is an advancement in the field and is consistent with the increasing body of literature supporting such an approach [50••]. Findings of the Methamphetamine Treatment Project continue to support the value of integrated treatment for co-occurring conditions, and especially the importance of training counseling staff to handle psychotic symptoms when needed [29•].

The Iowa Case Management Project was designed to supplement treatment interventions by providing outreach activities such as visiting clients in their homes, assisting with transportation to and from services, and providing emergency funds on a limited basis. Results from the project indicate that comprehensive case management is an effective intervention for improving employment status and lowering the incidence of depression [27].

While specific behavioral interventions are useful in the treatment of substance use disorders, medications also have an important role in treatment. Promising results are emerging for an agonist-type or 'replacement' strategy paralleling that for nicotine and opioid dependence. In a detailed review, Grabowski and colleagues [51••] have examined the current status of preclinical research agonist and antagonist pharmacotherapy strategies, and in particular the use of stimulant medications in cocaine dependence and amphetamine replacement strategies for amphetamine dependence. These authors concluded that the risks in a replacement/agonist-like strategy for stimulant dependence are manageable. Joint application of quality behavioral therapy and a potent stimulant, with appropriate monitoring procedures, should produce benefit and a reduction in risk compared with continuation of the usual patterns of stimulant abuse and dependence. Collaborative efforts of preclinical and clinical researchers will be important in the development of specific medications and conceptualization of optimal strategies, regimens, and preparation forms.

Conclusion

Progress, albeit rather slow, is being made toward developing effective treatment for methamphetamine dependence. Much work remains to be done, including the development of treatments for psychotic symptoms, the withdrawal syndrome, cognitive performance, neuronal damage, and structural brain alterations.

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Methamphetamine: An Update on Epidemiology, Pharmacology, Clinical Phenomenology, and Treatment Literature

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Abstract

Background—Despite initial reports of a decline in use in the early 2000s, methamphetamine remains a significant public health concern with known neurotoxic and neurocognitive effects to the user. The goal of this review is to update the literature on methamphetamine use and addiction since its assent to peak popularity in 1990s.

Methods—Specifically, we first review recent epidemiological reports with a focus on methamphetamine accessibility, changes in use and disorder prevalence rates over time, and accurate estimates of the associated burden of care to the individual and society. Second, we review methamphetamine pharmacology literature with emphasis on the structural and functional neurotoxic effects associated with repeated use of the drug. Third, we briefly outline the findings on methamphetamine-related neurocognitive deficits as assessed via behavioral and neuroimaging paradigms. Lastly, we review the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial and pharmacological treatments within the context of an addiction biology framework.

Conclusion—Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Keywords

methamphetamine; stimulants; addiction; medication development

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1. Introduction

Methamphetamine use remains a significant public health concern in the United States (U.S.) and worldwide. Research has greatly advanced our knowledge of the epidemiology, consequences, and treatment of methamphetamine use disorders since methamphetamine's peak in popularity in the 1990s. Thus, the goal of this review is to update the literature on methamphetamine use and addiction since its assent to popularity. To do so, we cover recent epidemiological reports, methamphetamine pharmacology, and briefly outline the neurocognitive deficits associated with chronic methamphetamine use. We also discuss the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial interventions and pharmacological treatments.

This review is intended to supplement recent, more comprehensive reviews of pharmacologic treatments for methamphetamine addiction (i.e., Brackins et al., 2011; Brensilver et al., 2013; Rose and Grant, 2008) by distinguishing medications that have been tested clinically for reducing methamphetamine use from medications that may be promising based on their anti-craving effects – yet, clinical trials are ultimately needed. A number of other areas of potential interest to the field are also expanded upon, such as the trends in methamphetamine use/abuse rates, associated costs to the individual and society, and recent debates regarding methamphetamine-related neurocognitive impairments. Furthermore, the present review differs from other methamphetamine reviews (e.g., Panenka et al., 2013) by incorporating this wide range of domains of interest and by highlighting the increasingly recognized role for the opioidergic system in the development (i.e., reinforcement), maintenance (i.e., craving), and treatment (i.e., naltrexone) of methamphetamine addiction as an area for greater study in methamphetamine-related research. Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Articles for inclusion in this review were identified through an extensive literature search conducted in January, 2014 (and repeated in March, April, and July, 2014) in the PubMed and national survey databases. Search terms included "methamphetamine" (or "amphetamine" where appropriate) and domain specific terms such as "pharmacokinetics," "neurocognition," and "treatment." Efforts were made to include the most recent reports within each section in order to provide an updated summary of the current knowledge of the field.

1.1 Epidemiology of Methamphetamine

Methamphetamine remains a widely used illicit drug in the U.S. Estimates from 2012 suggest over 12 million people in the U.S., ages 12 years and older (4.7% of total responders) have used methamphetamine in their lifetimes, 1.2 million people (0.4 %) reported using methamphetamine in the past year, and approximately 440,000 (0.2%) of those identified as past month users (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013a). Amphetamine-type simulants (ATS), of which methamphetamine is the most frequently used, are the second most commonly used class of illicit drugs worldwide (United Nations Office on Drugs and Crime (UNODC), 2012); approximately 0.7 percent of the global population (33.8 million people) aged 15-64 years-

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old, reported using an ATS in 2010 (UNODC, 2013). Importantly, these estimates appear to be growing, as stated in the 2013 World Drug Report, "The market for ATS appears to be expanding in terms of locations of manufacture and trafficking routes, as well as in terms of demand" (UNODC, 2013).

1.2 History of Methamphetamine Use in the United States

ATS have a long history of use in the U.S., going as far back as World War II when soldiers used ATS to reduce fatigue and suppress appetite. ATS were widely prescribed in the 1950s and 1960s as a medication for depression and obesity, reaching a peak of 31 million prescriptions in the U.S. in 1967 (Anglin et al., 2000), with a roughly estimated 9.7 million Americans identified as past-year users of amphetamines in 1970 (Rasmussen, 2008). The rates of ATS use declined following the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970, which reclassified amphetamine to a more restrictive schedule, thereby limiting its accepted medical use (Gonzales et al., 2010). After amphetamine was rescheduled, illicit manufacturers began making methamphetamine using phenyl-2-propanone ("P2P") and methylamine. However, after P2P became a Schedule II controlled substance in 1980, ephedrine and pseudoephedrine became the predominant precursors and large quantities of these chemicals were smuggled from Mexico into the U.S. (Maxwell and Brecht, 2011). The increase in production was followed by a dramatic increase in use, with methamphetamine specifically increasing in popularity during the 1990s and early 2000s (Rawson et al., 2002). For example, estimates from the 2002 U.S. National Survey on Drug Use and Health (NSDUH) suggest that over 210,000 individuals ages 12 and older tried methamphetamine for the first time in 1991, whereas 454,000 individuals did so in 1998 (SAMHSA, 2003). Following the passage of the Combat Methamphetamine Epidemic Act in 2005 which restricted public access to products containing pseudoephedrine, the rates of methamphetamine use finally began to decrease (Gonzales et al., 2010; Maxwell and Brecht, 2011; Maxwell and Rutkowski, 2008), as evinced by a drop to 192,000 of new methamphetamine users in 2005 (SAMHSA, 2006).

This decline in methamphetamine use estimates was short lived however, as illicit manufacturers of methamphetamine began to use the P2P processes once again (Maxwell and Brecht, 2011). Estimates from the 2012 NSDUH identify over 130,000 individuals as new methamphetamine users in 2012, and the number of past month users in 2012 (440,000 people or 0.2%) remained consistent with reports from the last five years (0.1-0.2%) (SAMHSA, 2013a).

Recent reports of production and supply indicate a probable rise of methamphetamine use in the near future. For example, the number of methamphetamine laboratories reported in the U.S. quadrupled from 2,754 in 2010 to 11,116 in 2011, and the amount of methamphetamine seized by the U.S. government increased from 15 tons in 2010 to 23 tons in 2011 (UNODC, 2013). Furthermore, production methods are refined on an ongoing basis to produce purer and more potent forms of methamphetamine, and at lower costs. Analysis of data from the System to Retrieve Information on Drug Evidence (STRIDE), which reflects evidence submitted to DEA laboratories for analysis from July 2007 through September 2010, indicates that the price per pure gram of methamphetamine decreased 61%, from $270.10 to

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$105.49, while the purity increased 114%, from 39% to 83% (Maxwell and Brecht, 2011). Together, the culmination of recent prevalence, production, and supply data forewarn of an impending increase in methamphetamine use in the years to come.

1.3 Current Rates of Abuse and Dependence

Although the prevalence rates of current methamphetamine use have been relatively stable over the past five years, the rates of methamphetamine use disorders in the U.S. are on the rise. In 2012, 535,000 (0.2%) individuals were estimated to meet the Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM–IV; American Psychiatric Association, 1994) criteria of stimulant abuse or dependence, a significant increase from the 329,000 (0.1%) in 2011 (SAMHSA, 2013a). This increase was especially pronounced among individuals aged 18-25 years, with 0.5% meeting criteria in 2012, up from 0.3% in 2011. Over 379,000 of individuals were estimated to meet dependence criteria for methamphetamine in 2012, as compared to 252,000 in 2011 (SAMHSA, 2013a).

Estimates from the Treatment Episode Data Set (TEDS), which provides information on admissions to substance abuse treatment facilities that are licensed or certified by state substance abuse agencies, suggest that treatment admissions for primary methamphetamine increased from 78,248 individuals ages 12 or older (4.4% of admissions) in 2001 to 154,364 individuals (8.1%) in 2005, but then decreased to 102,384 individuals (5.6%) in 2011 (SAMHSA, 2013b). The recently released TEDS data report a slight increase for 2012, with 116, 090 individuals (6.6%) being admitted for primary methamphetamine-related problems (SAMHSA, 2014).The rates of methamphetamine dependence appear to be roughly equivalent in men compared to women, with 53% of primary methamphetamine/ amphetamine admissions being male. Further, the majority of individuals admitted to treatment were non-Hispanic White (69%), followed by individuals of Mexican origin (12%; SAMHSA, 2014). Thus, methamphetamine dependence is largely a disorder of the White population; however, this may be a byproduct of the regional variability in methamphetamine use, which is currently greatest in the West and parts of the Midwest (NIDA, 2012).

1.4 Burden of Care Associated with Methamphetamine Use

In 2009, the RAND Corporation published the first national estimate of the economic burden of methamphetamine use based on information available for 2005 (Nicosia et al., 2009). They estimated the economic burden of methamphetamine use in the U.S. to be approximately $23.4 billion, which includes the costs associated with drug treatment, other health costs, the intangible burden of addiction and premature death, lost productivity, crime and criminal justice costs, child endangerment, and harms resulting from production. These intangible costs of addiction make up a substantial portion of the overall cost, at approximately $12.6 billion; which includes the costs associated with drug treatment at approximately $545 million, primarily delivered in the community-based specialty treatment sector ($491 million; Nicosia et al., 2009). These high costs are consistent with the TEDS data, which indicate that primary methamphetamine/ amphetamine admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/ residential treatment (16 % vs. 7 %) (SAMHSA, 2013b).

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In summary, methamphetamine use and the associated disorders constitute a significant burden to the individual and to society. Furthermore, the substantial time and resources devoted to the treatment of methamphetamine use disorders in the U.S. underscores the need for more efficacious, cost effective, and easily deliverable treatments.

2. Pharmacology of Methamphetamine

2.1 Chemistry of Methamphetamine

Methamphetamine, also known as metamfetamine, N-methylamphetamine, methylamphetamine, and desoxyephedrine, is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs. Methamphetamine exists in two stereoisomers, the land d- forms. D-methamphetamine, or the dextrorotary enantiomer, is a more powerful psychostimulant, with 3-5 times the central nervous system (CNS) activity as compared to l-methamphetamine, or the levoratary enantiomer (Ciccarone, 2011); however, both enantiomers influence dopamine release and can induce stereotypy (i.e., persistent mechanical repetition of speech or movement) and psychosis at high doses (Kuczenski et al., 1995). Illicitly, methamphetamine may be sold as pure d-methamphetamine (dextromethamphetamine) or in a racemic mixture, and presents as powder or crystalline form, the latter commonly referred to as "ice" or "crystal meth" (Cruickshank and Dyer, 2009). Crystalline methamphetamine typically refers to a highly purified form of d-methamphetamine which is intended for smoking, with similar effects to that from an intravenous dose (Cho, 1990). Further, crystalline methamphetamine is associated with an increased incidence of dependence, as compared to the lower purity forms (McKetin et al., 2006).

2.2 Molecular Pharmacology of Methamphetamine

Methamphetamine is a cationic lipophilic molecule which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho and Melega, 2002). Due to its structural similarity, methamphetamine substitutes for the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulate postsynaptic monoamine receptors (Cruickshank and Dyer, 2009). Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase (Sulzer et al., 2005), further enabling the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of methamphetamine act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008). The medial basal forebrain, the hippocampus, and the prefrontal cortex (PFC) represent noradrenergic regions of interest, with various functions related to arousal, memory consolidation, and cognitive

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processing, respectively (Berridge and Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). However, the wide distribution of monoamines throughout the CNS, interactions between the monoamine pathways, baseline dopamine (and likely other monoamine) functioning, and peripherally mediated effects of methamphetamine add to the complexity of methamphetamine's effect on the monoamine systems (Cruickshank and Dyer, 2009).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid systems in the establishment of reinforcement (Boutrel, 2008). Three families of endogenous opioid peptides have been identified (dynorphins, endorphins and enkephalins), each associated with a distinct polypeptide precursor (prodynorphin, proopiomelanocortin, and proenkephalin). These precursors produce a number of active ligands including β-endorphin, met- and leu-enkephalin, dynorphins, and neo-endorphins (Kieffer and Gavériaux-Ruff, 2002). Each ligand expresses a different affinity for each opioid receptor; for example, β-Endorphin binds with higher affinity to μ- than δ- or κ-opioid receptors (Mansour et al., 1995b).

Anatomically speaking, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc; Mansour et al., 1995a).

Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ- and δ-opioid receptors in the NAcc (Hirose et al., 2005; Murakawa et al., 2004), and by decreasing GABA-inhibition via μ- and κ-opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci and Williams, 1997; Shoji et al., 1999). Many non-opioid drugs of abuse are also known to interact with the endogenous opioid system (for a review see Trigo et al., 2010). For example, preclinical studies in rats have shown that ethanol, cocaine, and d-amphetamine increase extracellular levels of endorphins in the NAcc (Olive et al., 2001), and that ethanol-induced increases in extracellular levels of dopamine in the NAcc are modulated by endogenous opioid system processes (e.g., Acquas et al., 1993; Lee et al., 2005). In humans, the rewarding effects of alcohol have been shown to be mediated by alcohol-induced endogenous opioid release in the NAcc and orbitofrontal cortex (OFC; Mitchell et al., 2012). Further, tobacco use, nicotine dependence severity, and nicotine craving were associated with reduced binding potential of a μ-opioid receptor agonist ([^{11}C]-carfentanil) in a number of mesolimbic regions in an alcohol dependent sample (Weerts et al., 2012). Together, these reports are suggestive of a general mediating role for the endogenous opioid system in the rewarding properties of multiple drugs of abuse.

ATSs have also been shown to affect the endogenous opioid system, which may mediate some of the rewarding properties associated with acute ATS use (Boutrel, 2008). For example, acute amphetamine administration has been linked with increased β-endorphin levels in the nucleus accumbens (Olive et al., 2001), increased striato-nigral dynorphin-like

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immunoreactivity (Bustamante et al., 2002; Hanson et al., 1988), and changes in the endogenous opioid mRNA expression in the striatum (Hurd and Herkenham, 1992; Smith and McGinty, 1994; Wang and McGinty, 1995). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of methamphetamine-induced behavioral (locomotor) sensitization (Chiu et al., 2006), analogous to compulsive drug seeking behavior in humans (i.e., drug craving; Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford et al., 2006).

In sum, methamphetamine has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

2.3 Clinical Pharmacokinetics of Methamphetamine

Methamphetamine is largely metabolized in the liver, resulting in metabolites including amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, and 4-hydroxynorephedrine (Caldwell et al., 1972). It is then excreted by the kidneys, with the majority excreted as unchanged methamphetamine (30-50%), followed by up to 15% as 4-hydroxymethamphetamine, and 10% as amphetamine. Approximately 70% of a single oral dose is excreted in the urine within 24 hours (Cook et al., 1993; Kim et al., 2004). With repeated dosing, methamphetamine can accumulate in the urine, with one study showing detection 7 days after a regimen of four daily 10mg oral doses (Oyler et al., 2002). Based on the pharmacokinetic data reviewed below, the typical assessment of methamphetamine abstinence in clinical studies consists of urinalysis at 3-4 day intervals (i.e., twice weekly).

Methamphetamine is commonly smoked, injected, ingested, snorted, dissolved sublingually, taken rectally, or solubilized and consumed as a liquid. Smoking, the most common route of administration (NIDA, 2012), and intravenous injection result in the near-immediate euphoric sensation which typically lasts for several minutes, as opposed to intranasal and oral injection which take approximately 5 and 20 minutes to reach peak euphoric state. The "high" through intranasal and oral methods however, is reported to last 8 to 12 hours (Meredith et al., 2005). When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion (Caldwell et al., 1972).

2.4 Clinical Response and Withdrawal of Methamphetamine

Methamphetamine is a potent CNS stimulator. As such, the clinical response to methamphetamine administration at low to moderate doses (5–30mg) includes euphoria, arousal, reduced fatigue, euphoria, positive mood, tachycardia, hypertension, pupil dilation, peripheral hyperthermia, reduced appetite, behavioral disinhibition, short-term improvement in cognitive domains, and anxiety (for a review see Cruickshank and Dyer, 2009). At frequent and high doses, there is also evidence that methamphetamine can induce psychotic episodes (Hermens et al., 2009; Ujike and Sato, 2004).

Frequent use of methamphetamine results in a depletion of presynaptic monoamine stores, down-regulation of receptors, and neurotoxicity (Barr et al., 2006; Meredith et al., 2005),

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resulting in significant psychiatric withdrawal symptoms following abrupt cessation after periods of regular use. Symptoms of methamphetamine withdrawal include anhedonia, hypersomnia, irritability, anxiety, aggression, and intense cravings for methamphetamine (Cantwell and McBride, 1998; Meredith et al., 2005). Depressive symptomatology has been considered the hallmark of methamphetamine withdrawal, with depressive symptoms lasting beyond two weeks of abstinence (Zorick et al., 2010). The severity of the withdrawal syndrome appears to be related to the frequency of use, yet methamphetamine withdrawal largely resolves spontaneously (Newton et al., 2004), and usually within 14 days of abstinence (Zorick et al., 2010). Protracted withdrawal from methamphetamine may in turn take several weeks to resolve and poses a large obstacle to sustained recovery.

2.5 Neurotoxicity Associated with Chronic Methamphetamine Use

Repeated exposure to moderate to high levels of methamphetamine has been related to neurotoxic effects on the dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies (Cho and Melega, 2002). Although the precise mechanisms remain unclear, the culmination of evidence suggests that the high level of cytoplasmic dopamine released as a result of methamphetamine use leads to the accumulation of reactive oxygen species and severe oxidative stress on the neuron (Berman et al., 2008a). Results of non-human primates given doses of methamphetamine roughly equivalent to a typical human abuse pattern of use (0.5-2mg/kg given four times at 2-hour intervals), indicate that methamphetamine at this (typical) level of use produces long-term reductions in dopaminergic axonal markers in the brain, including decreased striatal DAT density (Villemagne et al., 1998). Human studies using positron emission tomography (PET) and magnetic resonance imaging (MRI) data also provide support for prolonged neurotoxicity following repeated methamphetamine use. Reductions in striatal DAT site density (McCann et al., 1998; Volkow et al., 2001b, 2001d), D2 receptor availability (Volkow et al., 2001a), VMAT-2 density (Johanson et al., 2006), and SERT density (Sekine et al., 2006), have all been reported, with some markers (i.e., DAT density) showing improvement following prolonged (greater than 12 months) abstinence (Volkow et al., 2001b). Neurotoxic effects have been associated with behavioral and cognitive changes, such as memory deficits and impaired psychomotor coordination associated with reduced DAT site density (Volkow et al., 2001d), and increased aggression associated with reduced SERT density (Sekine et al., 2006). Chronic abuse of methamphetamine is also associated with reduced markers of neuronal integrity and increased markers of glial content, possibly indicating the proliferation of glial cells following neural damage (Chang et al., 2007; Ernst et al., 2000).

Structural brain abnormalities among frequent methamphetamine users as compared to healthy controls have also been observed, including, but not limited to, reduced white-matter integrity and/or organization associated with depression severity and positive psychiatric symptoms (Tobias et al., 2010), reduced gray matter in the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004), reduced hippocampal volumes associated with poorer memory performance (Thompson et al., 2004), altered shape of the corpus callosum (Oh et al., 2005), and increased volumes of the putamen and globus pallidus (interpreted as a compensatory effect; Chang et al., 2005). As noted by Berman and colleagues (2008a),

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lower cortical gray matter density or volume is the most consistently reported structural abnormality in amphetamine users, and studies assessing striatal gray matter report larger volumes in amphetamine abusers when compared to healthy controls, although the latter may reflect a compensatory response to initial neurotoxicity (Berman et al., 2008a).

A number of functional brain abnormalities have been observed in recently abstinent chronic abusers of methamphetamine. Using glucose metabolism as a marker of functional activity, regions of abnormally high relative activity include the amygdala, ventral striatum, and lateral orbitofrontal cortex (OFC), whereas abnormally low activity was observed in the medial PFC and cingulate cortex (London et al., 2004). Furthermore, glucose metabolism in the anterior and middle cingulate gyrus and the insula was negatively correlated with error rates on an auditory vigilance task in recently abstinent (4 to 7 days) methamphetamine abusers (London et al., 2005). Relative higher global and parietal cortex glucose metabolism has been noted to accompany continued abstinence (Berman et al., 2008b; Volkow et al., 2001c), along with relatively lower metabolism in striatal and thalamic regions (Volkow et al., 2001c; Wang et al., 2004). Importantly, some degree of recovery has been observed in the neocortical regions (Berman et al., 2008b) and thalamus (Wang et al., 2004) following one and nine months of abstinence, respectively.

3. Neurocognitive Functioning Associated with Chronic Methamphetamine Use

Chronic methamphetamine use has been associated with discrepancies in numerous cognitive processes dependent upon fronto-striatal and limbic circuits. However, differentiating preexisting deficits from methamphetamine-induced cognitive deficits poses significant challenges (Dean et al., 2013), and concerns regarding the interpretation of these discrepancies and their clinical significance have been raised (Hart et al., 2012). Despite this, the preponderance of evidence from preclinical, cross-sectional human, and brain imaging studies supports the assertion that methamphetamine abuse does indeed cause cognitive decline in at least some individuals (i.e., individuals at the age of early-to-middle adulthood; Dean et al., 2013) and that some cognitive/behavioral changes may be the result of methamphetamine neurotoxicity (Bortolato et al., 2009). Further, individual difference variables such as age, education level, and genotype appear to moderate the relationship between methamphetamine use and cognitive deficits (Dean et al., 2013).

With respect to the specific cognitive domains potentially affected, a meta-analysis of 18 studies found medium effects of methamphetamine use disorders on processes including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions. Small, yet significant, effects were also observed on measures of attention/working memory, language, and visuoconstruction (Scott et al., 2007).

A small number of these cognitive processes have been further examined using functional neuroimaging procedures in chronic methamphetamine users (for a review see Aron and Paulus, 2007). For example, the brain correlates of learning and cognitive control in methamphetamine abusers have been investigated using a color-word Stroop task

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administered during functional magnetic resonance imaging (fMRI). On this task, methamphetamine abusers display reduced reaction-time (RT) adjustments and reduced PFC activity following conflict (i.e., incongruent) trials (Salo et al., 2013, 2009), and reduced RT, increased error rate, and reduced activation of the right inferior frontal gyrus (IFG), supplementary motor cortex/anterior cingulate gyrus, and the anterior insular cortex during the incongruent condition (Nestor et al., 2011). Using a reversal learning task and PET in a preclinical sample, vervet monkeys given a chronic, escalating-dose regimen of methamphetamine revealed associations between the change in response to positive feedback and individual differences in the change in dopamine D_2-like receptor availability in the striatum, assessed pre- and post-methamphetamine regimen (Groman et al., 2012); thus advancing D_2 specific alterations of the dopaminergic system as a plausible neurobiological pathway subserving some of the disturbances in learning observed with repeated methamphetamine use.

Methamphetamine use disorders are associated with differential brain activity during decision-making, as assessed via fMRI. Methamphetamine abusers displayed reduced activation in the right IFG and the left medial frontal gyrus during a two-choice prediction task (where only 50% of the responses are reinforced with a correct response outcome), and a decrease in dorsolateral PFC (dlPFC) and right OFC activity in the active compared to control conditions, as opposed to the increase of activation in these areas observed in the healthy controls (Paulus et al., 2002). In a follow-up study using the same task, recently abstinent (average 25 days) individuals with methamphetamine dependence displayed reduced activation of the OFC, dlPFC, anterior cingulate cortex (ACC), and parietal cortex irrespective of the outcome, and attenuation of specific "success-related" patterns of brain activation as compared to healthy controls (Paulus et al., 2003). Furthermore, the degree of activation in the right middle frontal gyrus, middle temporal gyrus, and posterior cingulate during the two-choice prediction task in early remission (3-4 weeks abstinent) was predictive of relapse during a one-year follow-up (Paulus et al., 2005).

Methamphetamine dependence has also been associated with maladaptive reward-related decision-making, as indexed via steeper rates of temporal discounting ("delay discounting") (Hoffman et al., 2006). Contrasting "hard choices", where roughly equivalent preference is obtained for the immediate and delayed reward choices, and "easy choices", in which the choices differ dramatically in value and preference, revealed less activation in the precuneus, right caudate nucleus, ACC, and dlPFC in recently abstinent (2-8 weeks) individuals with methamphetamine dependence (Hoffman et al., 2008), and less activation of the left dlPFC and right intraparietal sulcus in active methamphetamine abusers (Monterosso et al., 2007), as compared to healthy controls. Furthermore, methamphetamine dependent individuals undergoing treatment display disrupted risk-related processing, a component of decision-making, on the Risky Gains Task in both the ACC and insula (Gowin et al., 2013).

In summary, methamphetamine use disorders are associated with specific task-related behavioral and neural processing differences across a number of cognitive domains, which appear to be moderated by individual difference variables. Importantly, evidence is accumulating to suggest some of these differences are associated with altered dopaminergic

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processing (Groman et al., 2012) and clinically meaningful outcomes (Paulus et al., 2005), suggestive of a functional role for these cognitive differences in the development and perpetuation of methamphetamine addiction.

4. Clinical Presentation of Methamphetamine Use Disorders

A methamphetamine use disorder represents a complex psychiatric condition characterized by a set of maladaptive behaviors which result in clinically significant functional impairment (American Psychiatric Association, 1994, 2013). A diagnosis made using the DSM-IV criteria necessitates the experience of at least 1 symptom of abuse or 3 symptoms of dependence occurring within a 12-month period (American Psychiatric Association, 1994), whereas the fifth edition of the DSM (DSM-5) combines these criterion (with a few notable changes) to form a single "methamphetamine use disorder" with an added severity specification (American Psychiatric Association, 2013). The DSM-specified criteria include maladaptive behaviors such as "continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of methamphetamine", the development of "tolerance" and "withdrawal," and "persistent desire or unsuccessful efforts to stop or cut down or control methamphetamine use."

The two most notable changes to the DSM-5 criteria include the removal of "legal problems" and the addition of "drug craving" to the symptom list. The addition of "craving" as a possible symptom represents an effort to increase consistency between DSM-5 and the International Classification of Diseases (ICD-10; World Health Orgainization, 2010), as well as acknowledgment of a vast amount of scientific research highlighting the importance of craving for understanding the pathogenesis and maintenance of addiction (e.g., Robinson and Berridge, 1993, 2001). Specific to methamphetamine addiction, research suggests individuals with this disorder exhibit cognitive performance deficits that are more pronounced during exposure to methamphetamine-related cues (Tolliver et al., 2012), and that level of craving for methamphetamine is associated with neural and behavioral measures of self-control (Tabibnia et al., 2011), together suggestive of a strong neural relationship between craving and clinically relevant behavioral markers of addiction. Furthermore, methamphetamine craving has been observed to be present for at least 5 weeks into abstinence, rendering the user particularly vulnerable to relapse during 7 to 14 days of abstinence (Zorick et al., 2010), and is a significant predictor of subsequent use during outpatient treatment (Galloway and Singleton, 2009; Hartz et al., 2001). Craving beliefs, or interpretations and decisions about cravings, have also been shown to predict relapse in a sample of regular methamphetamine users (Lee et al., 2010). On this basis, methamphetamine craving has been advanced as a surrogate marker of methamphetamine dependence (Galloway and Singleton, 2009). As with other substance use disorders, methamphetamine addiction is considered a chronic and relapsing disorder characterized by neurobiological changes that subserve the observed functional impairment in the individual (Koob et al., 2004).

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5. Treatment of Methamphetamine Use Disorders

At present, few effective options exist for individuals seeking treatment for methamphetamine use disorder, and to date these options have been limited to psychosocial interventions. Twelve-Step programs, such as Narcotics Anonymous, remain a common intervention pursued by many individuals with methamphetamine use concerns (Galanter et al., 2013) despite a lack of evidence supporting the efficacy of these programs as a stand-alone treatment (Donovan and Wells, 2007; Shearer, 2007). There is some, albeit modest, evidence to suggest that other psychological interventions are effective for stimulant users (Knapp et al., 2007; Shearer, 2007; Vocci and Montoya, 2009). However, the majority of the treatment efficacy research has been done with cocaine abusing populations, and given the known differences between individuals seeking treatment for methamphetamine versus cocaine (i.e., age of first use, route of administration, frequency of use, demographics, and prior exposure to treatment; Huber et al., 1997), it remains unclear whether the efficacy of these interventions is generalizable to individuals with a methamphetamine use disorder.

5.1 Psychosocial Treatments

A systematic review of cognitive and behavioral treatments as applied specifically to methamphetamine use disorders concluded that good clinical outcomes are achieved with Cognitive-Behavioral Treatment (CBT; with and without Motivational Interviewing [MI]) and Contingency Management (CM) therapies involving the systematic use of reinforcement (Lee and Rawson, 2008). A number of caveats must be considered when interpreting these conclusions however, such as the durability of treatment effects (especially with respect to CM programs). Furthermore, the effectiveness of psychosocial interventions is compromised by poor rates of treatment induction and retention (Shearer, 2007), and methamphetamine-related cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments ineffective (Baicy and London, 2007).

5.2 Pharmacologic Treatments

Given these important caveats of psychosocial interventions, and the heavy focus on the neurobiology of methamphetamine dependence, attention has shifted to the development of efficacious pharmacotherapies for methamphetamine addiction (NIDA, 2005). At present, no medication is approved by the U.S. Food and Drug Administration (FDA) for use in methamphetamine dependence. Numerous classes of medication are currently under study, primarily in small clinical trials (for a recent focused review see Brensilver et al., 2013). Medications presumed to have potential for the treatment of methamphetamine addiction frequently target dopaminergic, serotonergic, GABAergic, and/or glutamatergic brain pathways (for a review see Vocci and Appel, 2007), as well as opioidergic pathways (e.g., Brensilver et al., 2013). Additionally, cognitive enhancing medications such as modafinil (an analeptic drug with known cognitive-enhancing properties) have garnered attention given the known cognitive deficits associated with chronic methamphetamine use (e.g., Ghahremani et al., 2011).

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5.2.1 Medications associated with reduced methamphetamine use—A focused review on pharmacological treatments for methamphetamine/amphetamine dependence identified only three double-blind placebo-controlled trials that have shown positive results for reducing use of the substance (Karila et al., 2010). The first two trials found treatment effects within a specific subpopulation of users; namely buproprion was associated with a reduction of methamphetamine use among baseline light, but not heavy, methamphetamine users (identified in a posthoc analysis; Shoptaw et al., 2008), and modafinil combined with CBT was associated with reduced methamphetamine use within a small sample of HIV+ gay men dependent on methamphetamine (McElhiney et al., 2009), although recent trials have not found strong support for a direct effect of modafinil on abstinence outcomes (e.g., Anderson et al., 2012; Heinzerling et al., 2010). The third trial found support for reduced amphetamine use and greater abstinence rates with naltrexone treatment (50mg) in a sample of amphetamine-dependent individuals (Jayaram-Lindstrom et al., 2008).

Since the review, a few medications have received support for reducing methamphetamine use, namely mirtazapine, topiramate, and naltrexone. Specifically, 12-weeks of mirtazapine treatment combined with CBT/MI counseling was associated with significant reductions in methamphetamine use (percent positive urines at the week 12 visit) in a sample of methamphetamine-dependent men who have sex with men (MSM) (Colfax et al., 2011).

Topiramate was associated with more patients achieving a 50 or 25 percent reduction in baseline level of methamphetamine use in large multi-site clinical trial; however, no effects on total abstinence (negative urines during 6-12 week follow-up) were observed (Elkashef et al., 2012). Further analysis of this data identified a small subgroup of patients who exhibited consistent reductions or achieved abstinence during follow-up, which were associated with topiramate treatment. This subgroup consisted of individuals who were more likely to have discontinued methamphetamine use (i.e., have a negative last urine) during the week prior to randomization (Ma et al., 2013), suggesting that topiramate may function best for relapse prevention. An additional study has found support for of the use of implant naltrexone for the treatment of problematic amphetamine use, noting patients with high levels of naltrexone (≥2 ng/ml) in their blood were 2.27 times more likely to be abstinent than patients with low naltrexone blood levels (<2 ng/ml; Grant et al., 2010). Clinical and preclinical laboratory models have also found support for reduced ATS use with naltrexone treatment. Specifically, clinical laboratory studies of naltrexone found reductions of both heroin and amphetamine use in a sample of individuals dependent on both substances (Tiihonen et al., 2012), and decreases in quality/liking ratings of administered amphetamine in a sample comprised of predominant cocaine users (Comer et al., 2013). Preclinical studies have observed naltrexone-related decreases in d-amphetamine and alcohol self-administration in adult rhesus monkeys (Jimenez-Gomez et al., 2011), and attenuated amphetamine-induced reinstatement with no effect on food taking behavior in the rat (Haggkvist et al., 2009).

The potential efficacy of naltrexone, an opioid antagonist with greatest affinity for the μ-opioid receptor and to a lesser but meaningful extent κ-and δ-opioid receptors (Ashenhurst et al., 2012), may lie in its ability to block drug-induced β-endorphin, and subsequent dopamine, release in the NAcc and through the blockade of drug-induced β-endorphin inhibition of GABAergic inhibitory interneurons in the VTA, as in the case of alcohol

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(Johnson, 2008; Zalewska-Kaszubska et al., 2006). The decrease in amphetamine-induced dopamine levels in the NAcc following blockade of the μ-opioid receptor by naltrindole (a selective 8-opioid receptor antagonist) and β-funaltrexamine (an irreversible μ-opioid receptor antagonist) provides support for this hypothesis (Schad et al., 1996). However, the efficacy of naltrexone treatment for methamphetamine dependent individuals remains unclear.

5.2.2 Medications associated with reduced methamphetamine craving—Given the putative role of craving in the maintenance of addiction, numerous medications have also been tested for their ability to alleviate methamphetamine craving. These medications include ondansetron (Johnson et al., 2008), methylphenidate (Miles et al., 2013), a combination of flumazenil, gabapentin and hydroxyzine (Ling et al., 2012), modafinil (Shearer et al., 2009), topiramate (Johnson et al., 2007), aripiprazole (Newton et al., 2008), sertraline (Zorick et al., 2011), and isradipine (Johnson et al., 2005). Unfortunately, none of these medications have shown associated reductions in subjective methamphetamine craving, and two of these medications, namely aripiprazole and sertraline, have even been associated with increased (Newton et al., 2008) or sustained (Zorick et al., 2011) craving following treatment, respectively.

Nevertheless, a few medications have shown potential to reduce methamphetamine craving. Treatment with dextroamphetamine, as a potential substitution therapy, has been shown to reduce craving, but not methamphetamine use, in treatment seeking individuals with methamphetamine dependence (Galloway et al., 2011). Rivastigmine, a cholinesterase inhibitor, was observed to reduce participant's endorsement of "Likely to Use Meth" when exposed to acute methamphetamine via intravenous infusion in a sample of non-treatment seeking methamphetamine dependent individuals (De La Garza et al., 2012). Buproprion, an antidepressant which inhibits the reuptake of dopamine and norepinepherine, has also been associated with reduced methamphetamine craving in response to video cues in a laboratory model of non-treatment seeking individuals with a methamphetamine use disorder (Newton et al., 2006). Nicotine has shown promise in rodent models of craving. Specifically, methamphetamine-seeking behavior was found to be attenuated by repeated nicotine administration during methamphetamine withdrawal. Further, this attenuating effect was antagonized by the nicotinic antagonist mecamylamine (Hiranita et al., 2004).

Naltrexone (12.5 and 50mg) was associated with a decrease in cocaine craving, but not positive subjective effects, during acute cocaine and d-amphetamine (versus placebo) administration in a sample comprised of predominant cocaine users (Comer et al., 2013). With respect to methamphetamine craving specifically, preclinical work suggests naltrexone inhibits reinstatement of drug-seeking behavior, a plausible marker of drug craving in the animal, induced by methamphetamine-associated cues in mice following 12 days of methamphetamine self-administration and extinction (Anggadiredja et al., 2004). These results were related to the changes in dopamine and dopamine metabolite levels (Lan et al., 2008), as well as to the binding of a D1 agonist and D2 antagonist (SKF38393 and sulpiride, respectively) to dopamine receptors in the striatum (Tien et al., 2007). Naltrexone was found to have no effect on methamphetamine-priming-induced reinstatement, possibly indicating a separate pathway for drug priming effects (Anggadiredja et al., 2004). Further, μ-opioid

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receptor knockout mice are unaffected by methamphetamine-induced behavioral sensitization (Shen et al., 2010), suggestive of naltrexone's mechanism of action in craving instatement. The blockage of methamphetamine-induced dopamine release in the mesolimbic dopamine system has been proposed as the neural mechanism underlying naltrexone's effect on cue-induced craving (Ashenhurst et al., 2012; Jayaram-Lindstrom et al., 2004); however, no study to date has been conducted in humans to test this hypothesis.

In summary, a number of pharmacotherapies are currently under study for the treatment of methamphetamine use disorders, many with promising preliminary results. Treatment development for methamphetamine use disorders, both behavioral and pharmacological, has been a challenging enterprise, yet consistent with the addiction field broadly (Litten et al., 2012) efforts to refocus the field towards medications with novel therapeutic targets hold considerable promise for this complex disorder.

6. Conclusions and Future Directions

Methamphetamine, a potent central nervous system stimulant, continues to pose a significant public health problem in the U.S. and worldwide. At present, the burden of care associated with methamphetamine use far exceeds what would be expected given the prevalence estimates, underscoring the pervasive impairments associated with methamphetamine use and addiction. Importantly, the culmination of recent prevalence, production, and supply reports warn of the potential for a “second wave” of increased methamphetamine use and associated problems, thus indicating the immediate need for advancements in basic and clinical methamphetamine research.

Through its actions on the brain's major dopaminergic, noradrenergic, serotonergic, and opioidergic pathways, repeated use of methamphetamine is associated with significant neurotoxic effects and neurocognitive deficits, with only a few of such effects known to remediate following sustained abstinence. Thus, early identification of problematic methamphetamine use and effective treatment implementation is critical to successful outcomes. Unfortunately, the available treatments for methamphetamine dependence are at best only modestly effective. There is modest evidence for the efficacy of psychosocial interventions, cognitive behavioral therapy (CBT) in particular; however, these treatments are time-intensive, expensive, and the outcomes are relatively poor at longer follow-up periods. Furthermore, there are no medications currently approved by the FDA to treat methamphetamine use disorders.

Following what appears to be a sequence of failures in medication development for methamphetamine dependence, the field has engendered renewed interest in the development of medications with novel molecular targets (e.g., enndocanabinoid and opioidergic systems, neuroinflammation; Brensilver et al., 2013; Snider et al., 2013; Vocci and Appel, 2007). Increasing evidence for the opioidergic system's role in the development (i.e., via reinforcement mechanisms) and maintenance (i.e., craving) of stimulant addiction has advanced pharmacologic agents targeting this pathway as plausible treatments for methamphetamine use disorders. Further, the few medications that have shown some promise for the treatment of methamphetamine use disorders, namely buproprion, modafinil,

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and naltrexone (as identified by this review), may exhibit greatest effectiveness through novel mechanisms such as enhancing the effectiveness of existent psychosocial interventions (e.g., via decreasing cognitive impairment) and by targeting intermediate phenotypes of addiction (e.g., relapse prevention/craving) (NIDA, 2005). Much more targeted, well-controlled research is indicated to fully understand the mechanisms and potential efficacy of these agents in the treatment of methamphetamine use disorders specifically, particularly given that these medications were commonly studied in small trials, distinct subpopulations, and/or predominately amphetamine using samples.

A number of gaps remain in the treatment literature for methamphetamine addiction. As described above, research is critically needed in pharmacologic treatment development (NIDA, 2005), particularly with novel targets and potentially novel delivery systems (e.g., vaccines; Kosten et al., 2014). By integrating basic neuroscience into treatment development research, one may elucidate how these novel interventions function to reduce methamphetamine use. This would allow in turn for the evaluation of neurotoxic and neurocognitive effects of prolonged methamphetamine use in the context of treatment outcomes and enable the identification of biomarkers with predictive validity. Further, given the poor retention rates, difficulties with treatment adherence, and overall poor outcomes associated with the interventions currently available, it is possible that the outpatient model employed for the treatment of many drugs of abuse is not suitable for methamphetamine addiction. If so, robust treatments studied within controlled inpatient/partial inpatient programs may prove more fruitful. As highlighted by this review and consistent with some conclusions reached by NIDA's Methamphetamine Addiction Treatment Think Tank (NIDA, 2005), research endeavors on the identification of biomarkers (to predict treatment response), relapse prevention (i.e., managing craving and stress), and remediation of associated cognitive impairment are advanced as crucial gaps in the knowledge base. Future research that can systematically address these gaps are thought to provide a roadmap for effective treatment development for methamphetamine addiction.

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Highlights

- Methamphetamine continues to pose a significant public health problem in the U.S.
- The review provides an update to the literature on methamphetamine use and addiction
- Current treatments for methamphetamine dependence are only modestly effective
- Future directions include development of medications with novel molecular targets

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Brain dopamine neurone 'damage': methamphetamine users vs. Parkinson's disease – a critical assessment of the evidence

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Abstract

The objective of this review is to evaluate the evidence that recreational methamphetamine exposure might damage dopamine neurones in human brain, as predicted by experimental animal findings. Brain dopamine marker data in methamphetamine users can now be compared with those in Parkinson's disease, for which the Oleh Hornykiewicz discovery in Vienna of a brain dopamine deficiency is established. Whereas all examined striatal (caudate and putamen) dopamine neuronal markers are decreased in Parkinson's disease, levels of only some (dopamine, dopamine transporter) but not others (dopamine metabolites, synthetic enzymes, vesicular monoamine transporter 2) are below normal in methamphetamine users. This suggests that loss of dopamine neurones might not be characteristic of methamphetamine exposure in at least some human drug users. In methamphetamine users, dopamine loss was more marked in caudate than in putamen, whereas in Parkinson's disease, the putamen is distinctly more affected. Substantia nigra loss of dopamine-containing cell bodies is characteristic of Parkinson's disease, but similar neuropathological studies have yet to be conducted in methamphetamine users. Similarly, it is uncertain whether brain gliosis, a common feature of brain damage, occurs after methamphetamine exposure in humans. Preliminary epidemiological findings suggest that methamphetamine use might increase risk of subsequent development of Parkinson's disease. We conclude that the available literature is insufficient to indicate that recreational methamphetamine exposure likely causes loss of dopamine neurones in humans but does suggest presence of a striatal dopamine deficiency that, in principle, could be corrected by dopamine substitution medication if safety and subject selection considerations can be resolved.

Introduction and objective

Methamphetamine (MA) is a dopaminergic stimulant drug widely used recreationally (for review, see Kish, 2014). MA can harm humans in part because some recreational users of the drug become addicted to the stimulant (Kish, 2008). Our own epidemiological findings from a large California cohort study also suggest, for example, that there is increased rate of all-cause mortality for MA users (standardized mortality rate, 4.67) in comparison with individuals of similar age, race and sex in the general population (Callaghan *et al.*, 2012b).

A still open question is whether chronic MA exposure can harm or 'damage' neurones in the human brain that use dopamine as a neurotransmitter – i.e., whether MA is 'neurotoxic' to those neurones. MA/amphetamine promotes release of dopamine from dopamine neurones in human brain (Laruelle *et al.*, 1995; Cardenas *et al.*, 2004; see also Pifl *et al.*, 1995; Rothman & Baumann, 2003; Sulzer *et al.*, 2005) through an action on both the plasma membrane dopamine transporter and the vesicular monoamine transporter. Experimental animal reports of MA-induced structural damage in dopamine neurones assessed by histological procedures (swollen/distorted axons, Fink-Heimer silver staining) and loss of dopamine markers (see Kish, 2014) predict that the stimulant, at some unknown, probably high dose, should also damage dopamine neurones in human brain. Historically, the general consensus in the animal literature has been that MA selectively damages dopamine nerve terminals (in the dopamine-rich striatum) but with a sparing of cell bodies in the substantia nigra (e.g., Ryan *et al.*, 1990); however, some experimental data suggest that (structural) damage may also extend to dopaminergic cell bodies in the nigra (see Ares-Santos *et al.*, 2014).

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The *objective* of this review is to evaluate, in a brief update summary, the evidence for and against the possibility that MA use in humans might be associated with damage to dopamine neurones. This is a summary update to an extensive review on the 'neurotoxicity' of MA up to approximately 2012/2013 (Kish, 2014). Whenever possible, MA findings will be compared with those in idiopathic Parkinson's disease, as Parkinson's disease remains the 'gold standard' dopamine deficiency disorder in the human. This manuscript is submitted in honour of Professor Oleh Hornykiewicz, who made the extraordinary discovery 56 years ago in Vienna of a brain dopamine deficiency in Parkinson's disease, and who is celebrating this year his 90th birthday.

We believe that effort aimed at understanding whether MA, a widely used stimulant, damages human brain is justified, in part, because this is a public health and forensic medicine issue and especially because the information obtained might inform new approaches to therapy. Further, demonstration of dopamine neurone damage in brain of recreational MA users would raise some concern that such damage might also occur in young people receiving the MA metabolite, amphetamine, for therapeutic purposes [e.g., attention deficit hyperactivity disorder (Ricaurte *et al.*, 2005)].

Dopamine

If dopamine neurone damage has occurred in human brain, it would be expected that levels of brain dopamine, as well as those of all dopamine markers, should be lower than those levels in persons who do not use MA.

Parkinson's disease: The dopamine deficiency discovery

The autopsied human brain investigation of Oleh Hornykiewicz in Vienna provided the proof that a brain dopamine deficiency is the defining biochemical feature of Parkinson's disease.

Hermann Blaschko, the British Council Scholarship supervisor of Hornykiewicz in Oxford England from 1956 to 1958, was the original 'inspiration' for Hornykiewicz to be involved in studies of dopamine: Whereas dopamine was previously felt to be only of limited interest as a metabolic intermediate in the pathway to noradrenaline, Blaschko speculated that dopamine might have 'some regulatory functions of its own which are not yet known' – and asked Hornykiewicz to continue to work with dopamine (Hargittai & Hargittai, 2005). Back in Vienna, Hornykiewicz, on his own, decided to focus on dopamine's possible role in the brain. Soon, armed with the experimental findings that brain dopamine was highly localized in the striatum (caudate and putamen) (Bertler & Rosengren, 1959; Sano *et al.*, 1959), and aware of Arvid Carlsson's pioneering animal work demonstrating that the 'tranquilizing' effect of reserpine, which can cause immobility in animals and a Parkinson's like syndrome (akinesia) in humans, could be abolished by the catecholamine precursor levodopa (Carlsson *et al.*, 1957), and the further demonstration that reserpine actually depletes the animal brain of catecholamines whereas levodopa preferentially restored the dopamine levels to normal (Carlsson *et al.*, 1958; Weil-Malherbe & Bone, 1958), Hornykiewicz abandoned his brain dopamine work in the animal (Holzer & Hornykiewicz, 1959) and moved quickly to the (autopsied) human brain itself [see Hornykiewicz (2010) for a review].

Logistical difficulties for the postmortem brain investigation were in part technical – a dopamine iodine assay set up in a 'semi-dark' basement of the Vienna Pharmacological Institute, and Dowex ion exchange columns requiring multiple football bladders – as a constant pressure pump was lacking. More difficult was obtaining a source of autopsied brain of Parkinson's patients (from Vienna's Wien-Lainz hospital) given that, at that time, neurochemical investigation of postmortem human brain was not considered to be a reasonable approach.

Hornykiewicz describes the moment of discovery:

> In April 1959, about eight weeks after reading the Bertler and Rosengrin report in Experientia (Bertler & Rosengren, 1959), we received the first brain of a patient who had died with Parkinson's disease. After carrying the sample of the caudate nucleus and putamen of this patient, together with control samples, through the extraction procedure, the thrilling moment of performing the von Euler and Hamberg colour (iodine) reaction arrived. Instead of the pink colour in the control samples, indicating presence of dopamine, the reaction vials containing the Parkinson material showed hardly a tinge of pink discolouration. For the first time ever, and before even placing the reaction vials into the colorimeter, I could see the brain dopamine deficiency in Parkinson's disease literally with my own naked eye! (Hargittai & Hargittai, 2005).

One year later Hornykiewicz had collected additional material and confirmed a striatal dopamine deficiency in a representative number of persons with Parkinson's disease (Ehringer & Hornykiewicz, 1960).

Professor David Marsden (1990) said this of the discovery in Vienna:

> The recent history of Parkinson's disease has been marked by momentous discoveries. Before the 1960s, the clinical features and neuropathology of the disorder had been established, anticholinergic drugs and stereotaxic surgery were popular, but the illness progressed relentlessly and was a cause of miserable disability. . .. The discovery of selective striatal dopamine deficiency in the parkinsonian brain in the early 1960s changed everything.

Methamphetamine users: One (Toronto) laboratory reports low brain dopamine

Given the extent of worldwide use of MA as a recreational drug, it is surprising that, to our knowledge, information on the status of dopamine in postmortem brain of chronic MA users is still limited to findings from our Toronto laboratory (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004). Part of the logistical difficulty is certainly explained by the need to obtain MA brain material from medical examiners/coroners – most have little or no 'extra' time to help out in a research investigation and, as a practical matter, often are not aware at autopsy that the decedent ever used MA until weeks (or more) later at which time blood drug measurements confirm drug use and the brain material has already been processed. Also, as the world has become much more litigious, medical examiners willing to go beyond their normal governmental duties and help out in a research study are now being asked to 'sign off' on provocative 'indemnification' statements in case of liability.

Our 2004 report (Moszczynska *et al.*, 2004) summarizes our findings (from 1990 to 2004) (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004) of dopamine measurement (by HPLC-electrochemical detection) in postmortem striatum of 20 chronic MA users and 14 control subjects having similar age and postmortem time. All MA users tested positive for MA and/or its metabolite amphetamine in blood and brain obtained at autopsy, meaning that the subjects had last

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used the drug 'recently' (within approximately 5 days preceding death). In addition, the MA data were compared with those of 12 subjects with neuropathologically confirmed Parkinson's disease (in collaboration with Professor Hornykiewicz), being the gold standard dopamine deficiency disorder (Wilson *et al.*, 1996b).

We found that dopamine levels in most of the individual MA users were below the lower limit of the control range in both the caudate and putamen striatal subdivisions. On average, dopamine concentration in the MA users was decreased by 61 and 50% in caudate and putamen, respectively. Previously, Hornykiewicz showed that the inter- (and intra-) regional striatal dopamine loss in Parkinson's disease has a highly characteristic pattern (Bernheimer *et al.*, 1973). As expected, in this new Parkinson's brain material, serving as a neurological control for the MA users, striatal dopamine levels were severely decreased in caudate (−82%) and to a greater extent in putamen (−97%) of the Parkinson's disease subjects with no overlap whatsoever between individual control and Parkinson's disease subjects (Moszczynska *et al.*, 2004). In principle, low striatal dopamine levels in the MA users could be explained by a loss of dopamine in intact neurones (e.g., caused by excessive MA-induced dopamine release and depletion) and/or by actual loss of dopaminergic neurones containing the neurotransmitter.

Unfortunately, our finding (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004) of low dopamine in some MA users still awaits replication by an independent laboratory and must therefore be considered 'preliminary'. The explanation for the lack of replication investigations is likely due in part to the practical difficulty in obtaining (frozen) autopsied brain of MA users from different medical examiner centres with the necessary short postmortem time. Further, recreational MA use in, for example, the United States is highly prevalent only in certain geographical areas (e.g., U.S. west coast). It should be noted, however, that 'many' (11) years passed before the 1960, Hornykiewicz dopamine deficiency in Parkinson's disease discovery (Ehringer & Hornykiewicz, 1960) was replicated in an independent laboratory (Fahn *et al.*, 1971), in which only two cases were analysed. The explanation for the replication delay in the Parkinson's disease literature could well be due, at least in part, to the appreciation in the scientific community that his findings just 'had to be correct' and did not require any replication.

Dopamine metabolite homovanillic acid (HVA)

Parkinson's disease: Striatal HVA is low, but not as low as that of dopamine

Following the 1960 discovery, there was some concern in the scientific community that the finding of low dopamine in Parkinson's disease might have been a pre- or postmortem artefact (Hornykiewicz, 1994). Hornykiewicz hoped to refute this proposition through demonstration of a 'control' neurochemical that was not decreased in brain of the subject: 'We continued to look for neurotransmitter parameters that were not reduced in Parkinson brain' (Hornykiewicz, 1993). Subsequent investigation, however, disclosed low brain levels in neurotransmitters noradrenaline and serotonin (Ehringer & Hornykiewicz, 1960; Bernheimer *et al.*, 1961), prompting this comment from Hornykiewicz: 'No help from noradrenaline and serotonin' (Hornykiewicz, 1992a).

Given data suggesting that the dopamine metabolite homovanillic acid (HVA) is 'stable' in autopsied human brain (Bernheimer, 1964), attention was turned to measurement of this dopamine marker. As expected, striatal HVA levels in Parkinson's disease were lower than those in the control subjects (Bernheimer & Hornykiewicz, 1965). Loss of this dopamine marker provided additional support for a dopamine deficiency in Parkinson's disease; however, as noted by Hornykiewicz, the magnitude of the striatal HVA reduction was less than that of dopamine (see below). This finding of increased (neurotransmitter turnover) ratio of dopamine metabolite vs. dopamine suggested a compensatory increase in activity of the remaining dopamine neurones in Parkinson's disease in which neurotransmitter synthesis, release and metabolism might be accelerated (Hornykiewicz & Kish, 1987). [This notion of 'neurochemical compensation' was later extended by Zigmond and colleagues in their elegant investigations employing an animal model of Parkinson's disease (Zigmond *et al.*, 1984).] The Pifl-Hornykiewicz team (see Pifl *et al.*, 2014) later obtained data suggesting that the increased HVA/dopamine ratio could also be explained in part by impaired dopamine sequestration in vesicles and consequent increased metabolism of dopamine.

Methamphetamine users: Striatal homovanillic acid concentration (and dopamine biosynthetic enzymes) is normal

Unlike the situation in Parkinson's disease, characterized by marked dopamine loss and reduced HVA, in postmortem brain of dopamine deficient MA users, we found that striatal HVA levels were surprisingly and distinctly normal, as were concentrations of two other dopamine metabolites (3,4-dihydroxyphenylacetic acid [DOPAC], 3-methoxytyramine [3-MT]) and two biosynthetic enzymes (tyrosine hydroxylase, dopa decarboxylase) (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004), which are all markedly decreased in Parkinson's disease (Zhong *et al.*, 1995; Wilson *et al.*, 1996b).

It is possible that normal HVA in the presence of low dopamine could be explained by greatly accelerated release and metabolism of dopamine (to HVA) in the MA users – all having recently used the stimulant. However, the lack of any substantial reduction in striatal HVA (or those of the other dopamine markers mentioned above), even in those MA users having very severely decreased dopamine, provides little support for any 'marked' loss of entire dopamine neurones in MA user brain, as is the case in Parkinson's disease.

Dopamine transporter

Parkinson's disease: Striatal dopamine transporter is, as expected, low

As expected, in both postmortem brain studies (Wilson *et al.*, 1996b) and imaging investigations of living brain (Frost *et al.*, 1993; Lee *et al.*, 2000), striatal levels of the dopamine transporter are decreased in Parkinson's disease as compared to those in matched controls. The loss of this dopamine marker provides further evidence supporting the loss of entire dopamine-containing neurones in Parkinson's disease.

Methamphetamine users: Striatal dopamine transporter is reduced: Why?

In 1996, we showed that levels of the striatal dopamine transporter, determined by both radioligand binding and Western blotting procedures, were decreased in postmortem brain of MA users (Wilson *et al.*, 1996a). This is the most replicated brain dopamine marker observation in the human methamphetamine literature, with similar findings observed in a postmortem brain immunohistochemical study (Kitamura *et al.*, 2007) and in seven independent PET/SPECT imaging studies of living brain (McCann *et al.*, 1998, 2008; Sekine

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et al., 2001, 2003; Volkow *et al.*, 2001a,b; Johanson *et al.*, 2006; Chou *et al.*, 2007; Schouw *et al.*, 2013; Yuan *et al.*, 2014).

The explanation for the dopamine transporter reduction in MA users is still argued (a compensatory phenomenon in response to low dopamine?) (see Kish, 2014) and could be explained by loss of the transporter protein (which can change in concentration independently of dopamine neurone changes; Wilson & Kish, 1996) or by loss of part or all of the neurone containing the transporter (see also below). The follow-up brain imaging investigation by Volkow *et al.* (2001a) suggests that the striatal dopamine transporter reduction can normalize with extended drug abstinence (see also Chou *et al.*, 2007; Volkow *et al.*, 2015).

Vesicular monoamine transporter (VMAT2)

Parkinson's disease: Striatal VMAT2 levels are, as expected, low

The vesicular monoamine transporter (VMAT2) is localized to the membrane of intraneuronal vesicles and is responsible for transporting monoamine neurotransmitters (dopamine, serotonin, noradrenaline) from the neuronal cytoplasm into the storage vesicles. Although VMAT2 is not specific to mammalian brain dopamine neurones, most VMAT2 in the dopamine-rich striatum is likely present in dopamine neurones (see Wilson *et al.*, 1996b; Frey *et al.*, 2001).

Like all dopamine markers mentioned above and examined to date, striatal VMAT2 levels, using binding of radiolabeled tetrabenazine analogues or immunoreactivity, is low in both postmortem (see Wilson *et al.*, 1996b; Tong *et al.*, 2011 and references therein) and living brain (by positron emission tomography, PET; Frey *et al.*, 1996; Lee *et al.*, 2000) of persons with Parkinson's disease.

Methamphetamine users: Striatal VMAT2 binding/ immunoreactivity is normal/near-normal or elevated

Striatal VMAT2 has been measured in human MA users in two postmortem brain investigations (Wilson *et al.*, 1996a; Kitamura *et al.*, 2007) and in a total of three brain imaging studies (Johanson *et al.*, 2006; Boileau *et al.*, 2008, 2016a). Taken together, the findings provide evidence for no or at most, a slight loss of VMAT2 in chronic human MA users.

In our own 1996 postmortem brain study, we found that striatal VMAT2 binding at a high saturating substrate concentration was normal in MA users (Wilson *et al.*, 1996a). Similarly, Kitamura *et al.* (2007), also in a postmortem brain investigation, found no statistically significant difference in VMAT2 protein (by immunohistochemistry) in humans exposed to MA, although a trend for a reduction was observed in nucleus accumbens and putamen.

In the first brain imaging study (PET), striatal VMAT2 binding (at a very low non-saturating radiotracer dose) was slightly (by 10%) reduced in MA users scanned when (reputedly) withdrawn for 3 years from the drug (Johanson *et al.*, 2006), whereas in the two more recent investigations (both from our laboratory), binding was *increased* in early abstinence (< 1 week) but was normal in those withdrawn for 7–15 days (Boileau *et al.*, 2008, 2016a). We interpret the increased VMAT2 binding in very early drug abstinence as explained by reduced competition between intravesicular dopamine and the VMAT2 radioligand at the VMAT2 site at which (we believe) dopamine is likely to be low in MA users who had recently taken the drug. This reduced competition between dopamine and the radiolabeled VMAT2 ligand (^{11}C-dihydrotetrabenazine) for the VMAT2 binding site (Tong *et al.*, 2008) likely explains increased VMAT2 binding in very early abstinence. (Similarly, striatal VMAT2 binding is slightly above normal in persons with dopa-responsive dystonia, characterized by low dopamine due to a metabolic defect in intact dopamine neurones; De La Fuente-Fernandez *et al.*, 2003.) In later MA abstinence, levels of dopamine might normalize to some extent, explaining the normal VMAT2 binding 1–2 weeks following drug withdrawal. As expected, striatal VMAT2 binding was markedly decreased in a small group of patients with Parkinson's disease, employed as a neurological control in the MA study (Boileau *et al.*, 2008).

The findings for the striatal VMAT2 dopamine marker in MA users (elevated to slightly decreased) differ from those for Parkinson's disease (markedly reduced) and raise further uncertainty whether loss of dopamine neurones is a feature of MA use in the human.

Substantia nigra cellularity

Parkinson's disease: Decreased number of 'dopaminergic' substantia nigra cell bodies

It would be expected that loss of entire neurones utilizing dopamine as a neurotransmitter – those originating in the human substantia nigra and innervating the dopamine-rich striatum – should be reflected by decreased number of substantia nigra compacta dopamine-containing cell bodies. As expected, Parkinson's disease is fundamentally characterized by loss of nigral cell bodies that contain dopamine markers (the pigment neuromelanin formed as part of dopamine metabolism; the biosynthetic enzyme tyrosine hydroxylase) (Bernheimer *et al.*, 1973; Hirsch *et al.*, 1988; Fearnley & Lees, 1991; Pakkenberg *et al.*, 1991; Rudow *et al.*, 2008). In general, the loss of nigral cell number (and nigral dopamine concentration; Hornykiewicz, 1963; Tong *et al.*, 2006) in Parkinson's disease is less than that of dopamine concentration in the nerve terminal regions of the caudate (about 80%) and putamen (> 95%) (Hornykiewicz, 1992b). This prompted Hornykiewicz to suggest that the primary degenerative process in Parkinson's disease might begin at the nerve ending – a 'retrograde degeneration' dying back phenomenon (Hornykiewicz, 1992b).

Methamphetamine users: No quantitative neuropathological data on nigral cellularity are available

As the formalin fixed tissue collected from multiple sources was not appropriate for quantitative cell counting, no quantitative assessment of the substantia nigra compacta cell bodies was conducted in autopsied brain of the MA users of our studies (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004). However, qualitative assessment of the substantia nigra in our studies by a neuropathologist experienced in histopathological examination of patients with degenerative movement disorders (including Parkinson's disease, progressive supranuclear palsy and multiple system atrophy) showed no 'obvious' loss of nigral cells in the MA users. Kitamura, in his neuropathological investigation of MA users in Japan, did not comment on brainstem changes in his case material (Kitamura *et al.*, 2007, 2010).

Brain gliosis as an index of neurotoxicity

As 'brain damage' can be commonly associated with activation and/or proliferation of glial cells, there has been interest in establishing whether brain astrogliosis or microgliosis is a feature of human MA

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users (see Tong *et al.*, 2014), as occurs in experimental animals who have received high doses of the stimulant (O'Callaghan & Miller, 1994; Thomas *et al.*, 2004). The special interest in this question is related to the possibility that brain gliosis, depending on the stage of damage, might be both helpful and/or detrimental (Sofroniew & Vinters, 2010; Streit, 2010) – allowing for the use of glial-specific therapeutics that could protect the MA-exposed brain from harm.

Parkinson's disease: Substantia nigra microgliosis – but astrogliosis still uncertain

As reviewed by Fellner *et al.* (2011), microgliosis in the degenerating substantia nigra is a common feature of Parkinson's disease. With respect to astrogliosis, the situation in Parkinson's disease is much less certain (see Bruck *et al.*, 2016) – and in our own study, levels of astroglial marker proteins in brain homogenates of persons with Parkinson's disease were generally normal (Tong *et al.*, 2015). In this regard, Halliday and Stevens (2011) have suggested that *decreased* astroglial response in Parkinson's disease might exacerbate the neurodegeneration.

Methamphetamine users: Brain gliosis status is uncertain

To our knowledge, studies of brain gliosis in human MA users are limited to a brain imaging study and two postmortem brain investigations.

In the first investigation Sekine *et al.* (2008) reported in a brain imaging (PET) study a massive increase (250–1500%) in binding of ^{11}C-PK11195, purportedly to activated microglial and astroglial cells, throughout the brain of MA users who had been withdrawn from the drug for at least 6 months. The data, however, are uncertain because of the high non-specific binding and difficulty in specific binding quantitation (see Tong *et al.*, 2014).

The second study included quantitative measurement of microglial and astroglial markers in postmortem brain of MA users (Kitamura *et al.*, 2010) with the obtained data generally 'mixed'. Thus, number of striatal microglial cells were normal (CR3/43 positive) or increased (glucose transporter-5 positive) and those of astroglial cells (glial fibrillary acid protein (GFAP) and S100B) were normal. Kitamura noted that there was no proliferation of activated microglia and that most astrocytes did not exhibit reactive changes.

Our own postmortem brain investigation employed a striatal brain homogenate approach in which concentrations of protein makers of microglial and astroglial cells were measured by Western blotting. Although protein levels of the glial markers were, as expected, elevated in brain of the neurological controls (multiple system atrophy), concentrations of intact glial proteins were normal in the MA group (Tong *et al.*, 2014). The only 'hint' of a glial disturbance was our finding (of uncertain significance) of increased brain levels of two partially degraded astrocytic protein markers (heat shock protein-27, vimentin) in the MA users.

The above three studies taken together suggest that the status of brain gliosis in human MA users is still uncertain.

Does methamphetamine cause clinical parkinsonism in the human?

If MA severely damages dopamine neurones, Parkinsonism should be a characteristic feature of at least a subgroup of humans who use MA. Assuming that MA users have a striatal dopamine deficiency, it might also be expected that a subgroup might be more susceptible to drug-induced Parkinsonism should they receive dopamine receptor blocking drugs for control of psychosis. However, suggestive evidence for the latter possibility appears limited to a single case report (Matthew & Gedzior, 2015).

Recently, we employed an epidemiological approach to address the above questions by making use of United States California statewide inpatient hospital data in which individuals with a MA/amphetamine related condition were followed up for up to 16 years to determine whether the MA group was more likely than a matched (appendicitis) group and a drug control (cocaine) group to show increased risk of developing Parkinson's disease. Consistent with our hypothesis, the MA, but not the cocaine group, had increased hazard ratio (HR, 1.76; 95% CI, 1.12–2.75) as compared with the proxy control group (Callaghan *et al.*, 2010, 2012a). More recently, Curtin *et al.* (2015) reported similar findings using a Utah Statewide population database of MA users who had a higher risk (HR, 2.8; 95% CI, 1.6–4.8) of developing Parkinson's disease. These longitudinal association studies do not provide 'proof' but are consistent with the possibility that MA might damage dopamine neurones in a subgroup of users in which Parkinsonism develops in middle/late age after some age-related loss of dopamine neurones. However, the findings also would suggest that only a very small proportion of MA users are subsequently diagnosed with Parkinson's disease.

Comment

Marked dopamine loss in some methamphetamine users could be 'harmful'

The objective of this review was to evaluate the available literature to establish whether MA might damage dopamine neurones in the human.

Employing the term 'damage' ('injury', 'harm') in a very general sense it is reasonable, we believe, to conclude that the dopamine loss in some MA users could cause some behavioural abnormality, perhaps limited to those individuals in which the reduction was near-total. Thus, we think it likely that subjects #448 (95% caudate dopamine loss) and #678 (97% caudate dopamine loss) of our study (Moszczynska *et al.*, 2004), who suffered a near-total loss of dopamine (95 and 97%, respectively) (which falls into the 'Parkinsonian range'), would have had some behavioural impairment caused by the very low dopamine. To our knowledge, no behavioural data are available for individuals affected exclusively by a loss of dopaminergic innervation to the caudate, or selectively to the putamen. However, Hornykiewicz has emphasized the different overlapping roles in the human in which dopamine innervation to caudate nucleus can be expected to control aspects of 'cognition', whereas that to the putamen (more affected than that to caudate in Parkinson's disease) is more likely involved in control of motor function (see Kish *et al.*, 1988). Given that the caudate nucleus is affected more by dopamine loss in MA users, we suspect that the major dopamine-related harm in these drug users might be cognitive difficulties that would persist as long as the dopamine deficiency is severe.

The possibility that any cognitive deficits in MA users are explained by low dopamine, however, remains to be established. In our brain imaging VMAT2 binding study of MA users in early abstinence, we did find an association between higher striatal VMAT2 binding (suggesting low dopamine) and poorer performance on some neuropsychological tests, but as a whole, only slight deficits in cognitive function were observed in the MA users as compared with control subjects (Boileau *et al.*, 2016a). Also, we recently reported that a brain imaging index of dopamine neurotransmission (amphetamine-stimulated changes in dopamine D3/D2

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receptor binding) was either *enhanced* (substantia nigra and globus pallidus) or unchanged (striatum), i.e., not blunted, in MA users withdrawn from the drug for at least 7 days (Boileau *et al.*, 2016b) – which would not be predicted in subjects having substantial dopamine reduction. However, the possibility still remains that dopamine neurone function in the striatum might be diminished in, but restricted to, those in very early abstinence when dopamine concentration is presumably much lower than that in later abstinence (Boileau *et al.*, 2016a) or after more severe chronic MA use (Boileau *et al.*, 2016b; see also Wang *et al.*, 2012).

But does methamphetamine cause loss of all or part of dopamine neurones?

Taking Parkinson's disease as the gold standard of a degenerative dopamine deficiency disorder, we can compare the loss of dopamine markers in Parkinson's disease vs. human MA users in our autopsied brain studies. As shown in Table 1, whereas levels of striatal dopamine nerve terminal markers, without any exception, are (moderately to severely) decreased in Parkinson's disease, concentrations of only two dopamine markers (dopamine, dopamine transporter) are below normal in MA users and with some (dopamine metabolites, biosynthetic enzymes, VMAT2) normal. Although levels of dopamine markers can change independently of changes in neuronal number, the findings that, unlike Parkinson's disease, not all striatal dopamine markers are reduced suggest that any dopamine neuronal loss in MA, if at all present, is unlikely to be substantial.

Dopamine substitution therapeutics in Parkinson's disease – any role in methamphetamine users?

From a public health perspective, most would agree that it is far more important to develop a therapeutic that will help people suffering from medical illnesses (e.g., Parkinson's disease, MA addiction) than to focus exclusively on the more limited 'academic' question whether the illness is or is not associated with a particular pattern of brain damage or pathology. Similarly, the new focus on the glial cell (an index of toxicity) in MA users is not primarily on its use as a 'toxicity' index, but rather on the hope that a helpful therapeutic could be developed based on neuroinflammatory actions/factors released by the glial cell.

As Hornykiewicz (2004) comments:

> The discovery of the profound lack of dopamine in the parkinsonian brain opened the door to the next and most consequential step: that from the 'dead (postmortem) human material to the live patient', i.e. to the use of levodopa as dopamine substitution treatment in Parkinson's disease. To put this idea into effect, in January 1961, I asked Walter Birkmayer, who was in charge of the neurological ward of the Municipal Home for the Aged in Lainz (Vienna) to try out levodopa in his permanently housed Parkinson patients.

In November 1961, Birkmayer and Hornykiewicz (Birkmayer & Hornykiewicz, 1961) published a short paper in 'Wiener Klinische Wochenschrift' providing the conclusive evidence that amelioration of parkinsonism could be achieved in patients with Parkinson's disease by intravenous levodopa, and that same month presented a dramatic film of the treatment to the Medical Association of Vienna.

> . . .The high expectations of those present were not disappointed by our presentation, which was followed by a spirited discussion. The lucidity of the rationale for the use of L-DOPA and its convincing, if not to say miraculous, effect in patients, produced the definite feeling in the audience filling the traditional lecture hall of the 'Billroth Haus' that they had just witnessed something that had all the marks of the out of the ordinary (Hornykiewicz, 2001).

The utility of levodopa is unquestionably established in Parkinson's disease. Although levodopa is not a 'cure' [Following on an early suggestion of Hornykiewicz that the cause of the degeneration in Parkinson's disease might be due to a 'reserpine-line' abnormality in dopamine storage (Hornykiewicz, 1964), the Vienna Hornykiewicz team later obtained postmortem data suggesting that a focus on abnormal dopamine vesicular storage in Parkinson's disease might actually point the way to a neuroprotective therapeutic (Pifl *et al.*, 2014)], this symptomatic treatment has transformed neurology practice.

Hornykiewicz reminds us:

> Today it is difficult for people, even for the young neurologists, to realize what the situation of the neurologists was before the L-DOPA era. The Parkinson patients were hopeless patients; they were crowding the chronic wards in the hospitals and they ended up completely stiff and bedridden, they could not get up, they could not feed themselves, they could not move, and had to be cared for until they died. The doctors were powerless. They could not do anything for those patients (Hargittai & Hargittai, 2005).

Assuming that the Toronto postmortem brain (Wilson *et al.*, 1996a; Moszczynska *et al.*, 2004) and brain imaging findings – suggesting that some MA users have a potentially harmful and severe brain dopamine deficiency – can be replicated and extended by independent groups, it seems reasonable to suggest that dopamine substitution therapy in methamphetamine users might help improve aspects of cognition subserved by caudate dopamine function in some drug users. It could also be argued that the striatal dopamine transporter reduction, consistently observed in brain of methamphetamine users, might actually represent a compensatory phenomenon to 'correct' the dopamine deficiency by increasing synaptic dopamine levels via decreased neurotransmitter uptake. It needs to be emphasized, however, that because of the possible interaction between levodopa and MA resulting in brain toxicity, levodopa should probably not be administered while residual MA is present (Boileau *et al.*, 2016a), making the usefulness of levodopa as dopamine substitution therapy in MA users logistically difficult. Also, whereas a severe striatal dopamine deficiency is present in all

TABLE 1. Brain dopamine marker changes in autopsied brain of patients with PD vs. MA users

Dopamine markers	PD	MA
Dopamine	Decreased	Decreased
Metabolites (HVA, DOPAC, 3-MT)	Decreased	Normal
Biosynthetic enzymes (TH, AADC)	Decreased	Normal
VMAT2	Decreased	Normal to slightly decreased
DAT	Decreased	Decreased
SNpc cellularity	Decreased	Unknown but no 'obvious' cell loss

3-MT, 3-methoxytyramine; AADC, aromatic L-amino acid decarboxylase; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; MA, methamphetamine; PD, Parkinson's disease; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; VMAT2, Vesicular monoamine transporter subtype 2.

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patients with Parkinson's disease, information on brain dopamine status – to identify those drug users having a severe dopamine depletion – is not yet available for MA users by using a brain imaging biomarker. Further, little information is available on the length of time in abstinence that a dopamine deficiency might persist, with our preliminary brain imaging data suggesting that a dopamine deficiency could be short-lived in some (low dose?) drug users (Boileau *et al.*, 2016a). Finally, perhaps MA users might only require low doses of levodopa to be of benefit. In this context, MA users might suffer dopamine loss but no loss of dopamine neurones, and therefore need only very low doses of levodopa to be of benefit, as is the case with dopa-responsive dystonia (Furukawa *et al.*, 1999).

Conclusions

We believe that it is premature, based on the available literature, to conclude whether recreational doses of MA cause or do not cause loss of, or damage to dopamine neurones in humans.

However, the fact that in our autopsied brain investigations not all dopamine markers were decreased in the dopamine-rich striatum of MA users – unlike the situation in Parkinson's disease (see Table 1) – leads us to speculate that MA, at the doses used by the subjects of our studies, was unlikely to have caused significant damage to brain dopamine neurones in the human. We further speculate that our findings in MA users who had recently used the drug, of very low striatal dopamine, as demonstrated by direct measurement (postmortem brain) and as inferred from high VMAT2 binding (living brain), are likely explained by a massive and acute drug-induced release and depletion of the neurotransmitter – that is at least partly reversible. Similarly, we feel that it is reasonable to speculate that the remarkably constant findings, by many different groups in the literature, of low striatal dopamine transporter in MA users is due to a compensatory (and reversible) attempt to maximize synaptic dopamine – a protein 'downregulation' in the absence of neurone loss. We emphasize the above are only speculations that may well need to be revised in future.

Assuming for the sake of argument that nigral dopamine cellularity is spared in MA users, we also acknowledge the practical difficulty in *quantitative* measurement of striatal dopamine nerve terminal number/density in human brain without depending on a dopamine 'marker' (to identify the neurone as 'dopaminergic') that has the potential of up- or down-regulation independently of any changes in neuropil concentration (for discussion, see Kish, 2014). In fact, we argue that this 'biochemical marker confound' will continue to raise uncertainty when interpreting findings in all studies of dopamine nerve terminal density in the human that aim to be 'quantitative'. (For example, what is the evidence that 60% loss of striatal dopamine, dopamine transporter, VMAT2, or dopamine biosynthetic enzymes equals 60%, or indeed *any* loss, of dopamine neuropil?). The lack of 'stability' of dopamine neurone markers is much less of an issue for those few animal studies that have *qualitatively* (only) assessed dopamine nerve terminal structural damage after MA exposure using classical histological neurotoxicity techniques (including electron microscopy) and reported evidence, for example, of tyrosine hydroxylase-positive neuronal processes with 'swollen and either empty of organelles or filled with membranous debris' (Ryan *et al.*, 1990) and 'vacuolated tyrosine hydroxylase-immunoreactive fibres with degenerating morphology' (Ares-Santos *et al.*, 2014). However, to our knowledge, such technically difficult investigations demonstrating structural damage to striatal dopaminergic terminals have yet to be conducted in postmortem brain of MA users. With respect to structural neuronal abnormalities in Parkinson's disease striatum, the literature also appears to be limited to qualitative reports of morphologically abnormal, 'short and kinked' (resembling Alzheimer's disease neuropil threads), or 'swollen', 'thickened non-beaded' tyrosine hydroxylase-positive neurites, which are probably undergoing degeneration, in the dopamine and tyrosine hydroxylase depleted striatum (Benzing *et al.*, 1993; Huot *et al.*, 2007; Bedard *et al.*, 2011; Kordower *et al.*, 2013) and pallidum (Jan *et al.*, 2000) of autopsied brains from patients with Parkinson's disease and a report of 'dystrophic neurites' in (biopsied) caudate nucleus of two patients with advanced Parkinson's disease – but with the authors' acknowledgement that it could not be determined whether the changes were actually dopaminergic (no dopamine marker staining was performed in the electron microscopy study) (Lach *et al.*, 1992).

This review also raises the general question of the applicability of experimental animal findings to the human condition.

As mentioned above, Oleh Hornykiewicz was encouraged by data from animal experiments (e.g., levodopa reversal of reserpine akinesia) but since the predictability of animal findings to the human is always uncertain, the definitive study had to await his investigation of dopamine in humans with Parkinson's disease. In the case of MA, there remains the question whether animal findings of dopamine neurone damage following very high-dose MA exposure (see Kish, 2014) will ever translate to human users of the drug. Had humans received the 'equivalent', often lethal, high doses of MA as those used in the animal studies, would we have observed in our autopsied brain studies more convincing evidence of dopamine neurone disturbance in which all examined dopamine markers would be markedly below normal and with prominent astroglial and microglial activation?

We do feel that our finding of low dopamine in MA users very recently withdrawn from the drug might have some clinical significance should the low dopamine (which we suggest is a reversible phenomenon) impact negatively on cognitive functioning and drug relapse. In this respect, the investigational use of levodopa as a dopamine substitution therapy in MA users in early drug withdrawal receives some general justification and would be a clear test of this hypothesis. However, more information on the safety and time course of any dopamine deficiency in MA users are needed, as well as the need to identify those users who are more likely to need and benefit from dopamine substitution therapy. Today, Parkinson's disease, owing to the efforts of Oleh Hornykiewicz in Vienna, still remains the gold standard of a levodopa-treatable neurodegenerative dopamine deficiency disorder.

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Addressing methamphetamine use in primary care

Methamphetamine, commonly referred to in New Zealand as "meth" or "P", is associated with high rates of personal and community harms. People who use methamphetamine have an increased risk of death due to overdose, suicide or cardiovascular causes. Any health interaction is an opportunity to discuss methamphetamine use if suspected and offer support to stop.

KEY PRACTICE POINTS:

- Health professionals need to be proactive when the opportunity arises in identifying people who have problems with methamphetamine use, as they may have little contact with health services and are unlikely to reveal their drug use without being asked
- Methamphetamine use is most prevalent among people aged in their 30s and under, and is more common in males compared with females and in Māori compared to people of other ethnicities
- People who use methamphetamine are at risk of dependency, psychosis and other mental and physical health complications, as well as financial, family, relationship and legal problems
- Counselling and support from a health professional, friends and family is currently the best approach for helping people to stop using methamphetamine
- Evidence does not support the use of any currently available pharmacological treatments to help patients quit or prevent relapses
- There are a variety of self-help resources and support programmes available that patients can be directed to

Methamphetamine is an addictive stimulant

Methamphetamine, also known as meth or "P", is a central nervous system stimulant that causes the release of dopamine, noradrenaline and serotonin.[1] It is the most potent form of amphetamine-type drug, and is ranked as the most harmful drug in New Zealand for dependent users.[2] The acute effects of ingestion, which resemble the "flight or fight" response, typically last four to eight hours and are similar to other psychostimulants, such as cocaine.[1] It can be produced in powder, pill or crystal formulations, the latter also referred to as "ice".

It produces a short-term high, followed by a crash

In survey data from Australia, the most common reasons people reported for taking methamphetamine were for the euphoric effect, to party or socialise, feel more confident or think more clearly.[3] One in ten people reported taking it to focus better at work.[3] Some people experience an increased libido with methamphetamine use, causing them to engage

in risky or prolonged sexual activities, and increasing their risk of sexually transmitted or blood-borne infections.[4]

Following an initial high, people who use methamphetamine experience a crash or "come down" in the following days, which can include exhaustion, prolonged sleep, depression and anxiety. Over the next weeks, users may experience difficulty sleeping or concentrating, headaches, muscle pain, mood swings, depression, anxiety and agitation, which can result in taking another dose to relieve symptoms of withdrawal.[1] Surveys have found that 20–30% of people using methamphetamine report being dependent, placing them at risk of long-term health consequences from chronic use.[5, 6]

People use it in a variety of ways, often alongside other substances

Methamphetamine is typically smoked in a glass pipe but can be swallowed, snorted or injected.[4] Patterns of use vary, but people who frequently use methamphetamine often take it in a binge of multiple doses a day, for up to four days in a row, sleeping very little during that time.[7] Methamphetamine is commonly used in combination with multiple substances, including cannabis, synthetic cannabinoids, GHB*, ecstasy, alcohol, methylphenidate, benzodiazepines and opioids such as tramadol.[8]

* Gamma-hydroxybutyric acid (GHB), also known by various other names such as "fantasy", "waz" or "mils", is a GABA B receptor agonist; it is sometimes used with methamphetamine and is associated with particularly severe withdrawal symptoms and overdose.

Methamphetamine use in New Zealand is not going away

In surveys conducted in New Zealand over the last decade, 1–2% of people have reported using an amphetamine, of which methamphetamine is one of the most common types. It is either imported illegally or manufactured from precursors.[9] Despite efforts to curb production and importation, usage rates are not going down, and methamphetamine is readily available; users in New Zealand report that they can get it within an hour.[5, 9]

In the most recent New Zealand Health Survey it was estimated that approximately 34,000 people aged 16–64 years had used an amphetamine in the past year (1.1% of the population).[9] The highest rates of use were in males (1.7% vs. 0.6% in females), people aged from 25–34 years (2.4%) and people of Māori ethnicity; after adjusting for age and sex differences between populations, Māori were 3.4 times more likely to have used amphetamines in the past year than non-Māori.[9] Analysis of drug metabolites in wastewater has found rates of methamphetamine use in Whangarei are two to four times higher than in Auckland or Christchurch, which is consistent with anecdotal reports of high rates of use in Northland.[10, 11]

Methamphetamine causes a range of health complications

Cardio- and cerebrovascular effects can occur during acute or chronic use, including hypertension, arrhythmias, myocardial infarction, stroke and heart failure.[7, 12] In an Australian study of mortality related to methamphetamine use from 2009–2015, 22% of deaths were attributed to "natural disease" in conjunction with methamphetamine toxicity. The most frequent natural disease was a cardiac condition or stroke.[13]

Neurochemical and functional changes occur in the brain with chronic use, including cognitive impairment and an increased risk of Parkinson's disease later in life.[12, 14]

Psychosis is estimated to affect three to four out of every ten people who chronically use methamphetamine.[15] This may manifest as unusual thoughts or statements, delusions of persecution or grandiosity, auditory, visual or tactile hallucinations, such as feeling something crawling on or coming out of the skin.[16] A small proportion of people can become aggressive or violent during an acute psychotic episode.[1] The risk of psychosis is related to the formulation, dose, frequency and duration of use of methamphetamine, however, once a person has had a psychotic episode they are more likely to experience further episodes at lower doses, referred to as "kindling".[16] Psychosis typically resolves as the drug effect wanes, however, in approximately one-third of people, symptoms persist for several months, and some people are subsequently diagnosed with schizophrenia.[16, 17]

Anxiety and depression can result from methamphetamine use, particularly during the "come down" period. Surveys in New Zealand have found that approximately one-quarter of people who frequently use methamphetamine are also taking antidepressants.[8] Suicidality is also more common among users of methamphetamine; 18% of methamphetamine-related deaths in Australia between 2009–2015 were suicide.[13] The impulsivity, disinhibition and psychosis associated with methamphetamine use is likely to be a factor in this. Assessing patients presenting with symptoms of anxiety or depression for the possibility of drug use should be a routine aspect of practice.

Dental problems are common in people with chronic use. It is likely that this is caused by the adverse effects of methamphetamine such as dry mouth, teeth grinding and clenching, lack of attention to oral hygiene and acid erosion due to the substance itself. Accelerated or unusual dental problems affect approximately 40% of people who chronically use methamphetamine.[18] This includes missing teeth, tooth erosion or extensive caries, lesions or abnormalities in the oral

mucosa, problems with the temporomandibular joint, or the need for dentures at a young age.[18]

Clinicians in primary care can help

Many people who use methamphetamine want to use less and are open to help from a general practitioner. The Global Drug Survey, which is an international data collection on use of illegal drugs, found that people who used methamphetamine reported high rates of wanting to use less or seek help, second only to tobacco users.[6] A survey in Australia of over 130 methamphetamine users reported that they would be most comfortable seeking help from friends or family members (38% of respondents), followed by health professionals such as a general practitioner or psychologist (29–31%).[3]

The crazed, violent image of a meth user is an extreme presentation

Methamphetamine users are often depicted in the media as violent or psychotic. However, while these instances can occur during acute intoxication, it does not reflect the typical circumstances of someone using methamphetamine.[19,20] People with mild to moderate problems with methamphetamine are more likely to be scared, anxious and on edge than violent, and can be treated in the community without health professionals or other support people being at risk of physical harm. In addition, the extreme image may cause some people to delay seeking help, as they believe their personal situation is not as bad as what they see in the media.[19,20]

General practitioners already have the skills needed

Reasons why general practitioners should enquire about the use of methamphetamine in patients they see include:[19,20]

- The best approach for helping patients to quit is counselling and psychological support, which general practitioners already use for helping patients with other problems such as addiction to smoking and alcohol
- General practitioners are familiar with the life circumstances of regular patients, allowing them to offer independent advice which is personalised to the patient's situation
- There can be a large delay between when people start having problems from their drug use to when they seek help. As general practitioners may be one of the few health professionals people using methamphetamine interact with, they can help to close that gap by asking patients about their drug use.
- Even if people are not ready to quit, general practitioners can help people to care for other aspects of their health and offer harm reduction advice (see: "Harm reduction for people who use methamphetamine").

Harm reduction for people who use methamphetamine [1]

- Emphasise that illicit drugs such as methamphetamine are unregulated and could contain other toxic substances
- Advise people injecting methamphetamine not to share needles and where to get clean ones, see: **www.nznep.org.nz/outlets**.
- Provide or prescribe condoms
- Explain the danger of combining methamphetamine with other substances, e.g. alcohol, other illicit drugs or prescription medicines
- Warn people of the symptoms of serotonin syndrome and to seek help immediately if they occur, particularly if they are taking a medicine which increases this risk, such as a SSRI, SNRI or tramadol
- Advise adequate hydration when using, e.g. at a dance party, and eating regular meals
- Advise extra attention to dental hygiene
- Warn against driving while under the influence of methamphetamine

For parents or caregivers using methamphetamine, advise them to:[1,4]

- Only use methamphetamine when their children are staying with a trusted caregiver
- Ensure they have sufficient recovery time before resuming their caregiver duties
- Keep supplies in a secure location and do not leave any paraphernalia associated with methamphetamine use around children, or talk about use around children
- Not to breastfeed if they are using methamphetamine regularly; if use is occasional, milk should be pumped and discarded until 48 hours have passed since using

Be proactive in asking patients about methamphetamine use

Non-specific indicators which may suggest methamphetamine use include:[1]

- Difficulty sleeping
- Feeling on edge or agitated
- Anxiety or depression
- Worsening symptoms of psychosis
- Aches or muscle pains
- Lethargy and tiredness
- Hypertension or chest pain
- Unexplained weight loss
- Lesions from excessive scratching due to itch or crawling sensations on the skin
- Needle marks (if injecting methamphetamine)
- Deteriorating dental health, e.g. missing teeth, tooth erosion or extensive caries
- Unusual behaviours or statements about themselves or their environment

Methamphetamine use may be difficult for patients to disclose due to the stigma of being a drug user or fear of authorities finding out. Points to consider when asking patients about methamphetamine use include:[19]

- Emphasise that the conversation is confidential and the only circumstances where a clinician would share the conversation with others is if the patient were a danger to themselves or others
- Use open-ended questions. For example, after asking about smoking or alcohol use, ask "what about anything else?", and repeat the question if necessary. People may disclose use of substances they feel are more acceptable first, e.g. admitting to cannabis use first and then methamphetamine use on further questioning.
- For a patient who has symptoms or signs suggestive of use, statements such as: "A lot of people who use meth feel like this when they're in withdrawal" or "I've treated patients who were coming off meth who tell me they felt like this", may help them to feel that they are not alone in their situation

Counselling and psychological support are the key interventions

Counselling and support from a health professional, whānau/family and friends is the best approach to encourage withdrawal and abstinence from methamphetamine. As little as two sessions of counselling can help improve abstinence rates for people with methamphetamine dependency.[20, 21] People must decide that they want to quit, and the role of the general practitioner is as a facilitator who helps them to come to that decision, then encourages perseverance once patients are attempting to quit (see: "Motivational interviewing can help people to reflect on their methamphetamine use").

Addiction specialists advise intervening in the first consultation when methamphetamine use is disclosed.[20] Clinicians may feel time-pressured to deal with the patient's presenting issue first and discuss their methamphetamine use at another time. However, people who use methamphetamine may have little contact with health services and engaging with the patient can set the scene for later change and help them avoid future harm.

Points to consider in the initial appointment include:

- Some people may disclose using methamphetamine, but have no intention of quitting – this can still be used as an opportunity to assess their health, e.g. investigations for blood-borne viruses for people who inject drugs or sexual health tests.[20]
- Offer harm reduction advice to reduce the risks associated with ongoing methamphetamine use (see: "Harm reduction for people who use methamphetamine")
- Discuss with patients whether they would like to be referred to a specialist service or community help programme (see: "Patient information and further assistance")
- Before patients leave, ask them to commit to a follow-up appointment and make a booking for them before they go and set up a reminder
- If appropriate, ask to include the patient's whānau/family in treatment plans and consider their point of view and experience of the situation

Withdrawal symptoms can take weeks to months to resolve

A typical time course of withdrawal symptoms for someone chronically using methamphetamine is shown in Table 1. Symptoms of craving, depression and anxiety usually substantially improve over the first two weeks and return to normal levels for that person after approximately five weeks, although symptoms may be prolonged in some people.[24]

Reassure patients that although they may feel very unwell, serious medical consequences from withdrawal are uncommon and supervision in an inpatient setting is typically not necessary.[1] In a minority of individuals withdrawal can be associated with suicidal ideation.[16]

A variety of support options are available to assist people undergoing methamphetamine withdrawal, including phone or text support and home-based withdrawal with help from a Māori health provider or addiction service (see: "Patient information and further assistance").

Motivational interviewing can help people to reflect on their methamphetamine use

"Move the frame of conversation from "telling" to "working with". Person-centred care is being able to genuinely empathise (understanding what it has been like), connect with the patient and have unconditional positive regard. It is essential in any interaction."

Motivational interviewing is a framework for facilitating open discussion about a topic and engaging change. There are four fundamental processes that are worked through:[22]

Engaging (whakawhanaunga): establishing a trusting relationship that sets the scene for open, honest and non-judgemental discussion.

Focusing (whakamārama): discussing the details of the specific issue, revealing the scope of the problem and any contributing factors.

Evoking (whakapuāwai): identifying the underlying motivations for change and the state of readiness for making that change

Planning (whakamaheretia): working together to formulate a plan for enacting changes.

The last stage of motivational interviewing may not be reached in the first or early sessions but following through the first three stages increases the likelihood of the patient engaging in behavioural change in the future.

An example of a motivational interview for a patient taking methamphetamine:

After establishing a connection and laying the foundation for an open discussion, ask the patient why they take methamphetamine and what they enjoy about it, followed by what the downsides are of taking methamphetamine. For example, ask: "Has a friend or family member ever been concerned about your use?".[23]

Summarise and repeat back to patients their responses, e.g. "So methamphetamine makes you feel more confident and have more fun in the weekend, but you feel worse early in the week and it is affecting your relationships".[23]

The purpose of this approach is to get patients to begin thinking about their use; even if they are not ready to stop, it encourages reflection on what they get out of using methamphetamine and what the costs are, in terms of their own personal health, effects on their relationships, or financial cost.

Ask patients how ready they are to make a change; e.g. "On a scale of one to ten, how ready are you to change your meth use?", and following with additional questions such as "what else needs to be done or happen to make you more ready?".[23]

If a patient is ready to change, or thinking about a change, they can be directed towards resources and support services (see: "Patient resources").

For further information, see:

"A model of short term intervention using motivational interviewing and cognitive behavioural therapy", In: Matua Raki, "Interventions and treatment for problematic use of methamphetamine and other amphetamine-type stimulants", available from:
www.health.govt.nz/system/files/documents/publications/meth-interventions-treatment-nov2010.pdf

"Takitaki mai: a guide to motivational interviewing for Māori", available from:
www.matuaraki.org.nz/uploads/files/resource-assets/Takitaki-mai-a-guide-to-motivational-interviewing-for-maori.pdf

Table 1: Time course of symptoms of withdrawal from methamphetamine.[1, 16 *]

Time period	Symptoms
Crash: First three day	■ Exhaustion ■ Prolonged sleeping ■ Low mood and energy, depression
Withdrawal: Severity of symptoms typically reduces over the first two weeks, but may last longer	Symptoms in the first week, ranked most common to least common: ■ Strong cravings to use again ■ Anxiety, irritability, agitation and mood swings ■ Aches and pains ■ Sleep disturbances, insomnia at night, sudden urge to sleep during the day ■ Difficulty concentrating ■ Depression and anhedonia ■ Headaches Common symptoms experienced up to a month or more: ■ Mood swings ■ Depression and anhedonia ■ Sleep disturbances and tiredness ■ Cravings

* Symptoms may be less severe and resolve quicker in people who have only used methamphetamine occasionally

Pharmacological treatment of withdrawal symptoms should be done with caution

Evidence does not support the use of any currently available pharmacological treatments to improve a person's chances of quitting methamphetamine or reduce rates of relapse.[25] Symptomatic pharmacological treatment of withdrawal symptoms may be considered in patients with severe symptoms that are unable to be managed with other interventions. Providing medicines such as benzodiazepines to people with an existing substance use disorder could lead to further misuse.[1] However, people may interpret a prescription to treat their withdrawal symptoms as a measure of acceptance and that their condition is serious enough to warrant treatment, or conversely that withholding a prescription is a form of punishment or disapproval.[1] Safeguards can be put in place to help to prevent inappropriate use of medicines (see: "Unintentional misuse of prescription medicines", bpac^{nz}, 2018, **www.bpac.org.nz/2018/misuse.aspx**).

Guidance in New Zealand recommends that a brief course of treatment with a benzodiazepine during acute withdrawal may be appropriate for people with severe distress or agitation.[1] In practice, quetiapine is often used as it is perceived to be more effective than a benzodiazepine in this scenario and less associated with misuse (although quetiapine still poses a risk). Initial doses of quetiapine should be small due to the risk of postural hypotension; a list of cautions can be found here: **www.nzf.org.nz/nzf_2176**

The use of an antidepressant such as a SSRI is unlikely to be useful for treating the symptoms of depression associated with withdrawal, as depressive symptoms are worst in the initial few weeks after stopping use and these medicines often require several weeks of dosing to take effect.[1] However, if depression persists, or is underlying to the substance misuse, antidepressant treatment is appropriate. N.B. Be aware of the potential for increased suicidal ideation during the methamphetamine withdrawal period, and in addition, an increased risk of serotonin syndrome in people who concurrently take a serotonergic medicine such as an SSRI, SNRI or tramadol with methamphetamine.

Patient information and further assistance:

- Referral to a local community alcohol and drug (CADS) or addiction service
- For people in Northland, the Te Ara Oranga Choice programme offers a one-day programme on methamphetamine use and withdrawal; referral is possible via Medtech: **https://community.northlanddhb.org.nz/NoP/**
- Patients and family members can get help from the "Meth Help" website and call centre:
  - **0800 METH HELP (0800 6384 4357)**
  - **https://drughelp.org.nz/a-bit-about-drugs/meth**

- Self-help booklets for withdrawing from meth can be downloaded from:
  - The Drug Foundation of New Zealand: **www.drugfoundation.org.nz/assets/uploads/2018-uploads/MethHelp-Handbook-2018-Edition.pdf**

    Hard copies for a practice to hand out can be ordered at: **https://drughelp.org.nz/a-bit-about-drugs/meth/guide-for-change-booklet**
  - Matua Raki: **www.matuaraki.org.nz/uploads/files/resource-assets/managing-your-own-withdrawal-a-guide-for-people-trying-to-stop-using-drugs-and-or-alcohol.pdf**

    www.matuaraki.org.nz/uploads/files/resource-assets/pd-off-self-guided-methamphetamine-and-ATS-withdrawal.pdf

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Article

Partial Recovery of Brain Metabolism in Methamphetamine Abusers After Protracted Abstinence

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Objective: Methamphetamine is a highly addictive drug of abuse that is neurotoxic to dopamine terminals. The authors recently reported that decreases in dopamine transporters (used as markers of dopamine terminals) in the striatum of methamphetamine abusers recover with protracted abstinence and that relative to comparison subjects, recently detoxified methamphetamine abusers have lower metabolism in the striatum and thalamus. In this study, the authors assessed whether metabolism recovers with protracted abstinence.

Method: Brain glucose metabolism was measured with positron emission tomography and [^{18}F]fluorodeoxyglucose in five methamphetamine abusers who were evaluated after both a short (<6 months) and protracted (12–17 months) abstinence interval, eight methamphetamine abusers tested only after protracted abstinence, and 11 comparison subjects who were not drug users.

Results: Significantly greater thalamic, but not striatal, metabolism was seen following protracted abstinence relative to metabolism assessed after a short abstinence interval, and this increase was associated with improved performance in motor and verbal memory tests. Relative to the comparison subjects, the methamphetamine abusers tested after protracted abstinence had lower metabolism in the striatum (most accentuated in the caudate and nucleus accumbens) but not in the thalamus.

Conclusions: The persistent decreases in striatal metabolism in methamphetamine abusers could reflect long-lasting changes in dopamine cell activity, and decreases in the nucleus accumbens could account for the persistence of amotivation and anhedonia in detoxified methamphetamine abusers. The recovery of thalamic metabolism could reflect adaptation responses to compensate for the dopamine deficits, and the associated improvement in neuropsychological performance further indicates its functional significance. These results suggest that while protracted abstinence may reverse some of the methamphetamine-induced alterations in brain function, other deficits persist.

(Am J Psychiatry 2004; 161:242–248)

The rapidly escalating abuse of methamphetamine places a sense of urgency on understanding its effects on the human brain and its medical consequences. Methamphetamine is a particularly problematic drug in that not only is it highly addictive but its administration to laboratory animals results in damage to dopamine terminals (1). Studies in the brains of methamphetamine abusers have also documented a significant loss of dopamine transporters, which have been used as markers of dopamine terminals (2–4). The dopamine transporter loss reported in methamphetamine abusers has been found to be associated with reduced motor speed and impaired verbal learning (3). Although early studies have proposed that methamphetamine-induced dopamine terminal damage is irreversible (5), subsequent studies in rodents (6, 7), nonhuman primates (8, 9), and humans (10) have revealed significant recovery with protracted abstinence. This suggests that methamphetamine-induced damage to the dopamine terminals may recover with protracted abstinence. However, while imaging studies have reported significant dopamine transporter increases with abstinence, this recovery has not been associated with the same degree of recovery in neuropsychological function. This could be explained if the dopamine transporter increases reflected 1) incomplete recovery of dopamine terminals, 2) enhanced arborization of viable dopamine synapses, or 3) methamphetamine's effects on other neurotransmitter systems that have less recovery. Using positron emission tomography (PET), we have previously shown that methamphetamine abusers have significant reductions in striatal and thalamic metabolism, which likely reflected the effects of dopamine terminal damage on projection regions (11). In this study, we assessed whether the decreases in striatal and thalamic metabolism recover with protracted methamphetamine abstinence and the extent to which recovery is associated with improved neuropsychological function.

For this purpose, we used PET and [^{18}F]fluorodeoxyglucose (FDG) to measure regional brain glucose metabolism, which serves as a marker of neuronal activity (12). The ini-

tial group (11), which comprised 12 methamphetamine abusers, was tested within 6 months of last methamphetamine use. They were followed and retested at least 9 months later if they remained drug free. Only five methamphetamine abusers were able to stay drug-free and were retested. Here we report the results from the repeated studies for these subjects and for eight additional methamphetamine abusers who were tested only once after having been abstinent for at least 9 months. The metabolic measures were compared with those of 11 age-matched comparison subjects who were not drug users and seven methamphetamine abusers whom we had previously tested within 6 months of abstinence (11). In parallel, we also measured selected neuropsychological functioning shown to correlate with dopamine transporter recovery (3).

Method

Subjects

Five methamphetamine users (three women and two men; mean age=29 years, SD=3) were evaluated twice, first after a short interval of abstinence (mean=3 months, SD=1.6) and then after at least 9 months of protracted abstinence (mean=14 months, SD=2). These five methamphetamine users were from an original group of 12 methamphetamine abusers (11) who were able to remain drug free for at least 9 months following the first PET scan evaluation. The seven other methamphetamine users of the original group of 12 who did not remain drug free constituted a short-term abstinence comparison group. In addition, we also evaluated eight additional methamphetamine users (six women and two men; mean age=36 years, SD=3) who were tested only once after having been detoxified for at least 9 months (mean=17 months, SD=10). The methamphetamine users fulfilled DSM-IV criteria for methamphetamine dependence (average methamphetamine use of at least 0.25 g/day at least 5 days per week for at least 2 years) and had been abstinent for at least 2 weeks. Subjects were excluded if seropositive for HIV or if comorbid neuropsychiatric disorder, medical illness, or current or past drug dependence other than methamphetamine and nicotine were found. Details for the screening procedures have been published (11). Methamphetamine users were enrolled in a California drug court monitoring rehabilitation program and were evaluated weekly or biweekly with drug screens, along with daily visits to the center, to ensure lack of regular drug use during the abstinence period.

The healthy comparison subjects were 11 volunteers (seven women and four men, mean age=31 years, SD=7) who were recruited by local advertisement. Exclusion criteria were the same as those for methamphetamine users except for dependence or abuse of methamphetamine. As for the methamphetamine users, a complete medical and psychiatric examination was performed in the subjects to ensure lack of medical, psychiatric, or neurological disease (G.-J.W., L.C.). The same screening laboratory tests as those given to the methamphetamine users (except for HIV serology) were obtained in these subjects. Prescan urine tests ensured absence of psychoactive drug use in all subjects. The protocol was approved by the Institutional Review Boards at Brookhaven National Laboratory, the State University of New York Stony Brook Medical Center, and the Harbor-UCLA Medical Center. All subjects gave written informed consent after the experimental procedure was explained and after they had read the consent form.

Scanning

Subjects were scanned by using FDG with a CTI-931 scanner. Details on procedures for positioning, arterial and venous catheterization, and quantification of radiotracer and transmission and emission scans have been published previously (13). Briefly, one emission scan (20 minutes) was taken 35 minutes after an intravenous injection of 4–6 mCi of FDG. During the study, subjects were positioned supine in the PET camera with their eyes open. The room was dimly lit, and noise was kept to a minimum. A nurse remained with the subjects throughout the procedure to ensure that they did not fall asleep during the study.

Neuropsychological Evaluation

For the methamphetamine users, we assessed performance on a selected set of neuropsychological tests that had previously been shown to be correlated with dopamine transporter levels (3). The tests were performed within 2 weeks of the PET studies and included 1) motor function tests (as quickly as possible, subjects walked in a straight line for a defined distance [timed gait test of gross motor function] and inserted pegs in small holes angled in different directions [grooved pegboard test of fine motor coordination]); 2) memory function tests (subjects had to learn and recall lists of unrelated words immediately, after a time delay, and after a distractor [Rey Auditory Verbal Learning Test]); and 3) attention tests (subjects had to identify the number associated with each one of the symbols arranged randomly in a row [Symbol Digit Modalities Test]).

Image Analysis and Modeling

Regions in the striatum (caudate, putamen) were obtained from three sequential planes, in the thalamus from two sequential planes, and in the occipital cortex from three sequential planes (as a control) using a template that we had previously published (13). We also computed a value for global metabolism by averaging the activity in the 15 planes scanned. To minimize the effects of overall changes in brain metabolism on the regional measures, we normalized them using the ratio of the region to the global metabolic measures ("relative" measures).

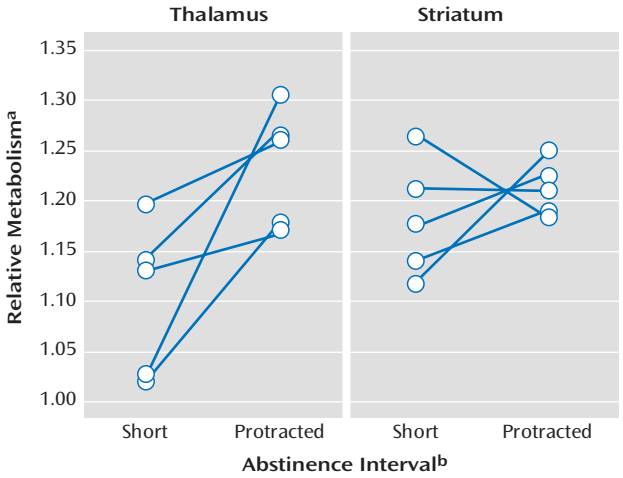
Statistical Analysis

Differences between metabolic measures obtained after short and protracted intervals of abstinence in the methamphetamine abusers were compared with paired t tests (two tailed). Pearson product correlations were used to assess the relationship between the changes in metabolism and the changes in neuropsychological performance between the first and second evaluation.

Differences in global and regional metabolism between the 11 comparison subjects, 10 methamphetamine users evaluated after protracted abstinence (the five methamphetamine abusers who were tested twice and five of the methamphetamine abusers evaluated only once during protracted abstinence), and the original sample of 12 methamphetamine users tested after a short interval of abstinence (seven women and five men; mean age=30 years, SD=6; mean days of abstinence=64, SD=40) were tested with unpaired t tests (two-tailed).

Differences between the two methamphetamine groups and the comparison subjects were also tested using the software package for statistical parametric mapping SPM 99 (14). Before the analysis, each subject's PET image was mapped onto the Montreal Neurological Institute template closely resembling the Talairach brain and smoothed via a Gaussian kernel with full width half maximum at 16 mm. The relative (normalized) image is obtained by dividing the signal level of each voxel with the global mean, which is the average signal level of all voxels in the PET image. The analysis was performed using both the absolute and the relative metabolic images. Pixels that were significantly different ($p<0.001$) from those in the comparison subjects were

FIGURE 1. Thalamic and Striatal Activity After a Short Interval of Abstinence and Protracted Abstinence in Five Methamphetamine Abusers



[a] Ratio of regional to global metabolism.
[b] Intervals of abstinence less than 6 months were classified as short; protracted abstinence referred to methamphetamine-free intervals of 12–17 months.

identified with respect to the Talairach and Tournoux stereotactic coordinates and displayed on the axial MR images. The threshold for the cluster size was set at 200 voxels, and only the corrected p values <0.05 at the cluster level were considered significant.

Results

Brain Metabolism in Methamphetamine Users After Short and Protracted Abstinence Intervals

Among the methamphetamine users who were evaluated twice, there were no differences in global metabolism measured after short versus protracted intervals of abstinence (mean=42.6 µmol/100 g per minute [SD=4.0] and 40.8 µmol/100 g per minute [SD=3.4], respectively) or in the absolute metabolic measures in the striatum, thalamus, or occipital cortex. As seen in Figure 1, comparison of "relative" metabolism measured after short and protracted intervals of abstinence showed significant increases in thalamic activity after protracted abstinence (mean=12%, SD=9%) (t=2.3, df=9, p<0.05) but no significant changes in the striatum (mean=2.7%, SD=6.7%) (t=1.3, df=9, p<0.23) or occipital cortex (mean=0.4%, SD=9%) (t=1.2, df=9, p<0.28).

As seen in Figure 2, analysis of the correlation between thalamic activity changes and changes in performance on neuropsychological tests for which we hypothesized an association with metabolic changes showed a significant association for timed gait, Symbol Digit Modalities Test, and delayed recall but not with the changes in the grooved pegboard task (r=0.26, df=3, p=0.68) or the immediate or interference recall (r=0.32, df=3, p=0.60).

Comparison of Healthy Subjects With Methamphetamine Users Tested After Short and Protracted Abstinence Intervals

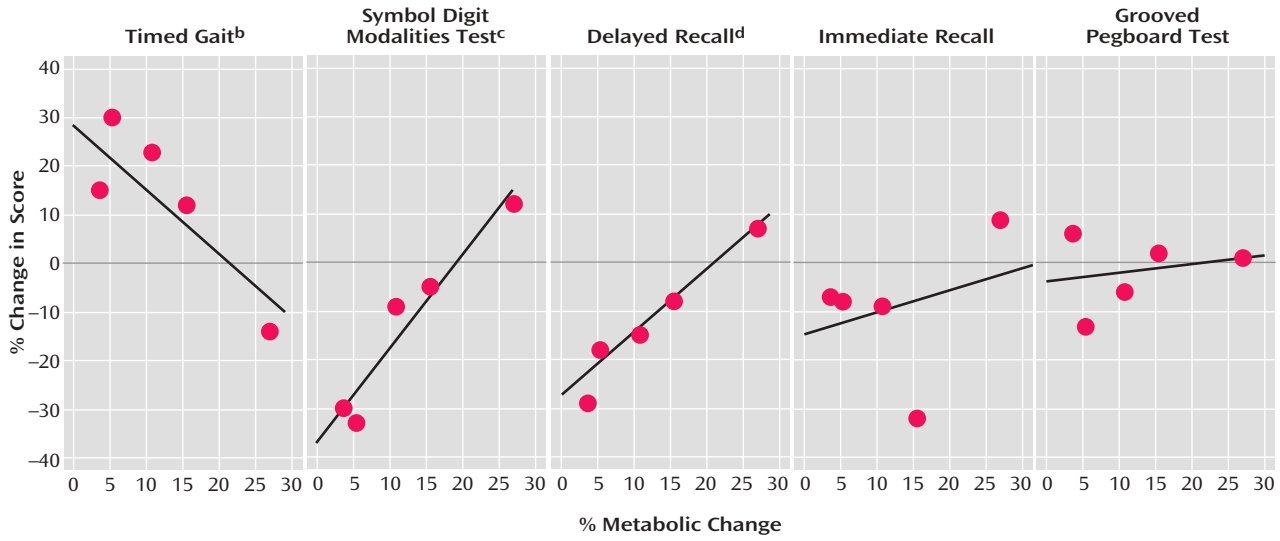
Absolute global brain metabolism was not significantly different in the methamphetamine abusers tested either after a short interval of abstinence (mean=38.5 µmol/100 g per minute, SD=8.5) or after protracted abstinence (mean=37.3 µmol/100 g per minute, SD=6.3) than in the comparison subjects (mean=33.8 µmol/100 g per minute, SD=7.4).

Regional changes were assessed by using the regional values normalized by the global measures. Compared with the relative metabolic measures seen in the striatum of the healthy subjects (caudate: mean=1.35, SD=0.06; putamen: mean=1.41, SD=0.09), the relative metabolic measures of the methamphetamine abusers were significantly lower after both a short abstinence interval (caudate: mean=1.2, SD=0.1 [t=–4.4, df=21, p<0.0002]; putamen: mean=1.31, SD=0.08 [t=–2.8, df=21, p<0.01]) and after protracted abstinence (caudate: mean=1.23, SD=0.09 [t=–4.4, df=22, p<0.0002; putamen: mean=1.29, SD=0.1 [t=–3.1, df=22, p<0.006]). Relative metabolism in the thalamus was significantly lower in the methamphetamine abusers after a short abstinence interval (mean=1.11, SD=0.08) relative to the comparison subjects (mean=1.31, SD=0.10) (t=–5.3, df=21, p<0.0001); however, thalamic metabolism in the methamphetamine abusers after protracted abstinence (mean=1.23, SD=0.09) did not differ from that of the comparison subjects.

The statistical parametric mapping analyses of the absolute metabolic values showed no differences between groups. The normalized metabolic values, with smaller intersubject variability, were also analyzed by using statistical parametric mapping, and the results were similar to those obtained with the region of interest method. The statistical parametric mapping analyses (Figure 3) yielded a large contiguous cluster (4,440 voxels) that encompassed three subclusters (left subcortical nuclei [including dorsal striatum, nucleus accumbens, and thalamus]: –8, 14, –6; left insula: –34, –6, –12; and right striatum: 14, 14, –6). The significance of this cluster is p<0.0001 (corrected at the cluster level).

For the region of interest method, metabolism in striatum was significantly lower in the methamphetamine abusers after both a short abstinence interval and protracted abstinence than in the comparison subjects. Similarly, the statistical parametric mapping analyses revealed significant decreases in the nucleus accumbens in the methamphetamine abusers whether they were tested after a short or protracted interval of abstinence. In contrast, thalamic metabolism, which was significantly lower in methamphetamine users after a short abstinence interval, was not different in the methamphetamine users after protracted abstinence relative to the comparison subjects. In addition, statistical parametric mapping revealed that relative to the comparison subjects, methamphetamine abusers had decreased metabolism in the left insular cor-

FIGURE 2. Correlation Between Changes in Thalamic Activity and Neuropsychological Test Performance in Five Methamphetamine Abusers Evaluated After Short and Protracted Intervals of Abstinence[a]



[a] Intervals of abstinence less than 6 months were classified as short; protracted abstinence referred to methamphetamine-free intervals of 12–17 months.
[b] r=0.88, df=3, p<0.05.
[c] r=0.96, df=3, p<0.009.
[d] r=0.98, df=3, p<0.005.

tex. The decreases in insular metabolism were more accentuated in the methamphetamine abusers tested after a short than after a protracted interval of abstinence.

Comparison Between Methamphetamine Users Tested After Short Versus Protracted Intervals of Abstinence

Relative metabolism in thalamus was significantly lower (t=–3,8, df=23, p<0.001) in the 12 methamphetamine abusers tested after a short abstinence interval than in the 13 methamphetamine abusers tested after protracted abstinence (N=13). Metabolism in the striatum did not differ between methamphetamine abusers tested after a short abstinence interval and those tested after protracted abstinence.

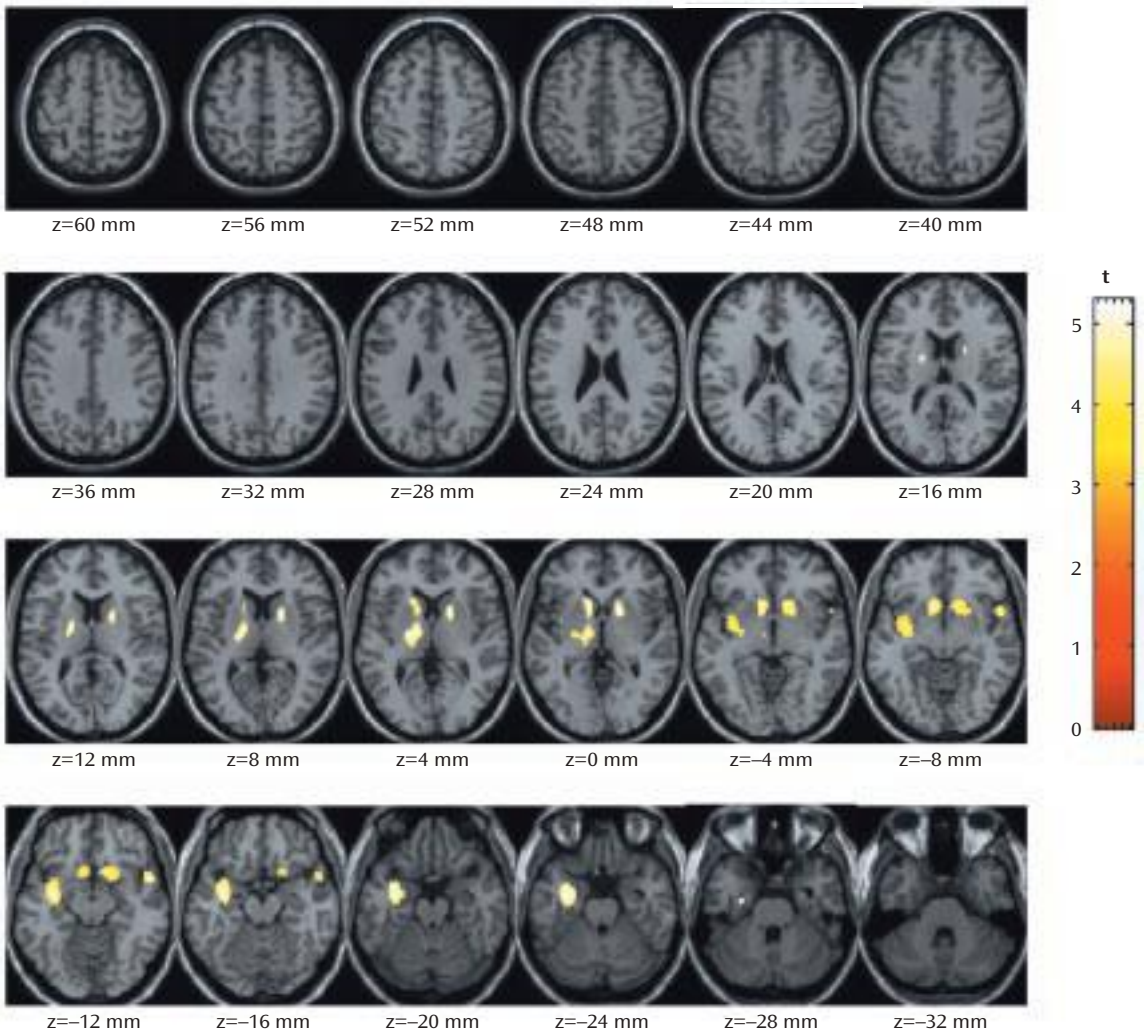
Discussion

Recovery of Thalamic but Not Striatal Metabolism With Protracted Methamphetamine Abstinence

In this study, we did not document recovery in striatal metabolism with protracted methamphetamine abstinence. Because metabolism predominantly reflects activity from terminal regions (15), the decreased metabolism in the striatum of methamphetamine abusers is likely to reflect disrupted dopamine cell activity. Indeed, preclinical studies have shown that methamphetamine induces damage to dopamine cells (16, 17), and in certain instances it can even produce cell death (18). The fact that the striatal changes remained after protracted abstinence suggests that the effects of methamphetamine on dopamine cells in the human brain are long-lasting. These results differ from our previous findings showing dopamine transporter increases toward normal levels in the striatum of methamphetamine abusers with protracted abstinence (3). Since the dopamine transporter PET measures serve mostly as markers for the dopamine terminals, this suggests that the dopamine transporter increases in the striatum likely reflect adaptation responses in viable dopamine terminals rather than reversal of methamphetamine-induced damage to dopamine cells. However, the long-lasting decreases in striatal metabolism could also reflect decreased activity from cortical efferents to the striatum, since methamphetamine is also neurotoxic to cortical excitatory cells (19).

In contrast to the striatal findings, this study documented significant recovery of thalamic metabolism with protracted abstinence in methamphetamine abusers who were able to stay drug free for at least 9 months after the initial evaluation. The recovery in thalamic metabolism with protracted abstinence could reflect improvement of neurotransmission in striatothalamic circuits. Indeed, in Parkinson's disease, where there is a significant loss of dopamine cells, improvement of dopamine neurotransmission with L-dopa treatment results in increases in thalamic metabolism (20). However, the increases in thalamic metabolism in the context of no recovery in striatal metabolism suggests that it may reflect adaptation responses in GABA cells, which are the main striatal efferents, in an attempt to compensate for dopamine deficits. The significant correlations observed between the increases in thalamic metabolism and the improvements on neuropsy-

FIGURE 3. Brain Regions in Which Methamphetamine Abusers (N=12) Evaluated After a Short Abstinence Interval Had Significantly Lower Metabolism Than Comparison Subjects (N=11)[a]



[a] Intervals of abstinence less than 6 months were classified as short. The number under each slice represents the distance from the anterior and posterior commissures. The threshold for cluster size was set at 200 voxels, and the significance threshold was set at $p<0.05$ (corrected at the cluster level). At this threshold, three significant subclusters are seen: 1) left subcortical nuclei, which includes the dorsal striatum, nucleus accumbens, and thalamus (–8, 14, –6); 2) left insula (–34, –6, –12); and 3) right striatum (14, 14, –6). Significance for the overall cluster: $p<0.0001$.

chological performance in some of the motor and verbal memory tasks further suggest that the thalamic changes with abstinence are functionally significant.

Comparison of Healthy Subjects With Methamphetamine Users Tested After Short and Protracted Intervals of Abstinence

Similar to the results obtained in the prospective studies assessing the effects of abstinence, the comparison in the cross-sectional studies revealed that relative to healthy subjects, striatal metabolism (including the nucleus accumbens) was significantly reduced in the methamphetamine users whether they were tested after a short or after a protracted interval of abstinence. Thalamic metabolism in the methamphetamine users, however, was lower only after a short abstinence interval, not after protracted abstinence. These results further corroborate that there is significant recovery of thalamic metabolism but persistence of decreased striatal metabolism with protracted methamphetamine abstinence.

The persistent reduction in metabolic activity in the striatum and nucleus accumbens could underlie some of the long-lasting deficits reported in abstinent methamphetamine abusers (21). In particular, the reduced activity in the nucleus accumbens could underlie the persistence of amotivation and anhedonia in detoxified methamphetamine abusers.

Changes in Insular Metabolism With Abstinence

The methamphetamine abusers also showed reduced metabolism in the insular cortex, which was much more accentuated in the subjects tested after a short abstinence

interval than in those tested after protracted abstinence. The insular cortex is a region neuroanatomically connected with limbic structures and autonomic centers (22), and imaging studies have suggested its involvement in drug addiction (23–26). Structural imaging studies have reported reduced volumes in temporal insula in stimulant drug abusers and have suggested that this might be a brain region particularly sensitive to the neurotoxic effects of stimulant drugs (27).

Limitations

There are several limitations to this study. First, the small number of subjects who were able to remain abstinent for more than 9 months in our study may not be representative of subjects with protracted abstinence. Thus, further studies with larger sample sizes are required to compare the degree of regional brain metabolic recovery and neuropsychological improvements between methamphetamine abusers who are able to stay drug free and those who are not in order to assess the generalizability of the findings from this study and its prognostic implications. Second, since we previously found whole brain metabolism to be significantly increased in methamphetamine users who had been abstinent for 2 weeks to 35 months (11), the current finding of only a nonsignificant trend for increases in global brain metabolism in methamphetamine users tested during protracted detoxification may be due to insufficient sample size. If whole brain glucose metabolism is indeed higher in the methamphetamine users, this could contribute to the observed lower relative rates in striatum. Third, since the urine toxicology tests were performed randomly within a 2-week period, it is possible that some of the methamphetamine subjects were using the drug intermittently but were not detected. However, these subjects visited the rehabilitation center daily, received cognitive behavior therapy, and knew that if they relapsed they would be sent to jail, which minimized the chances that they took drugs during the detoxification period. Fourth, we chose only a small number of neuropsychological tests (those that were found to correlate with dopamine transporter recovery [3]) in order to avoid multiple comparisons and intercorrelations among tests. Future studies using a more comprehensive battery of neuropsychological tests should provide better assessment of improvements in other cognitive domains. Last, we excluded subjects who had relapsed during the follow-up studies; it might have been instructive to evaluate whether this group of subjects would have persistent brain metabolic abnormalities.

Summary

The results from this study provide evidence that there is some functional recovery (as assessed by regional brain glucose metabolism) in the thalamus and insula but not in the striatum with methamphetamine abstinence. The recovery in the thalamus was associated with some degree of recovery of neuropsychological performance, indicating that it is functionally significant. The findings from these studies have implications in the treatment of methamphetamine abusers, for they suggest that protracted abstinence and proper rehabilitation may reverse some methamphetamine-induced alterations in brain function.

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Nicotine and Methamphetamine Share Discriminative Stimulus Effects

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Abstract

Background—Nicotine and methamphetamine are both abused in similar settings, sometimes together. Because there are known interactions between central nicotinic acetylcholine receptors and dopamine receptors, it is of interest to characterize the nature of the interaction of these two compounds in vivo.

Methods—The purpose of this study was to characterize the extent to which these two compounds produce similar discriminative stimulus effects and to identify pharmacological mechanisms for their interaction. Male Sprague-Dawley rats were trained to discriminate methamphetamine or nicotine from saline. First, the ability of methamphetamine and nicotine to cross-substitute in rats trained to the other compound was tested. Subsequently, the ability of a dopamine antagonist (haloperidol) and a centrally-acting nicotinic antagonist (mecamylamine) to block the discriminative stimulus effects of methamphetamine and nicotine were also tested.

Results—Nicotine fully substituted in methamphetamine-trained rats, but methamphetamine only partially substituted in nicotine-trained rats. In nicotine-trained rats, mecamylamine fully antagonized the discriminative stimulus effects of nicotine, but haloperidol had no effect. The partial substitution of methamphetamine was partially attenuated by haloperidol, but not altered by mecamylamine. In methamphetamine-trained rats, mecamylamine failed to antagonize the discriminative stimulus effects of methamphetamine, but haloperidol fully blocked the methamphetamine cue. Mecamylamine blocked the ability of nicotine to substitute for methamphetamine, but haloperidol had no effect.

Conclusions—These results indicate that nicotine and methamphetamine share discriminative stimulus effects in some subjects and that the two compounds do not act at the same site, but produce their interaction indirectly. These findings suggest that these two compounds might be at least partially interchangeable in human users, and that there are potentially interesting pharmacological reasons for the commonly observed co-administration of nicotine and methamphetamine.

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Contributors:
Drs. Gatch and Forster, and Ms. Flores designed the study. Ms. Flores and Dr. Gatch collected data and performed statistical analyses. Dr. Gatch managed the literature searches and summaries of previous related work, and wrote the first draft of the manuscript. All authors contributed to have approved the final manuscript.

Conflict of Interest:
All authors declare that they have no conflicts of interest.

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Keywords

methamphetamine; nicotine; mecamylamine; haloperidol; nicotinic acetylcholine receptor; dopamine receptor; co-abuse; drug-discrimination; rat

1. Introduction

Methamphetamine and nicotine are commonly used together (Goldsamt et al., 2005; Yen and Chong, 2006), yet the interaction of these two substances has been little studied. There are known interactions between central nicotinic acetylcholine receptors and dopamine receptors in the central nervous system e.g. (e.g., Quarta et al., 2006; Wonnacott et al., 2005), which provide possible mechanisms for the co-abuse of methamphetamine and nicotine. Because of this, it is of interest to characterize the nature of the interaction of these two compounds. Drug discrimination studies provide a useful tool to characterize the abuse liability of compounds, particularly with regard to their subjective effects (Balster, 1991; Stolerman, 1993). The subsequent sections will review the pharmacological mechanisms of the discriminative stimulus effects of methamphetamine and nicotine, and then possible mechanisms by which the two could interact.

1.1. Mechanisms of the discriminative stimulus effects of methamphetamine

Compounds that increase dopamine levels in the synapse (including dopamine releasers, uptake inhibitors, and D1-like and D2-like receptor agonists) all substitute for the discriminative stimulus effects of methamphetamine (Czoty et al., 2004; Munzar et al., 1999a; Munzar and Goldberg, 2000; Tidey and Bergman, 1998). Similarly, D1 and D2 receptor antagonists block the methamphetamine discriminative stimulus (Munzar and Goldberg, 2000; Tidey and Bergman, 1998). In contrast, adrenergic and serotonergic uptake inhibitors do not substitute for methamphetamine (Czoty et al., 2004; Munzar et al., 1999a; Munzar and Goldberg, 1999; Tidey and Bergman, 1998). Beta adrenergic agonists and antagonists fail to substitute or block the stimulus effects of methamphetamine (Munzar and Goldberg, 1999). Alpha-2 adrenergic compounds and various 5-HT agonists (5-HT_{1A}, 5-HT_2, 5-HT_3) produce at best partial substitution or small leftward-shifts in the dose response for methamphetamine discrimination (Munzar and Goldberg, 1999; Munzar et al., 2002; Munzar et al., 1999b). These findings indicate that the discriminative stimulus effects of methamphetamine are mediated mostly by the dopamine system, as dopaminergic compounds have robust effects in subjects trained to discriminate methamphetamine, whereas adrenergic and serotonergic compounds have only a modest ability to alter the stimulus effects of methamphetamine.

1.2. Mechanism of the discriminative stimulus effects of nicotine

The discriminative stimulus effects of nicotine are primarily mediated by central nicotinic receptors, such that agonists at these receptors substitute in nicotine-trained rats, and mecamylamine blocks the discriminative stimulus effects of nicotine (Miyata et al., 1999; Rosecrans, 1989; Stolerman, 1988). Other receptors also contribute to the stimulus effects of nicotine, dopamine receptors producing the largest effect. In general, dopamine transport blockers and D1-like agonists including cocaine, GBR-12909, bupropion, nomifensine, apomorphine, and SKF-82958 have produced partial substitution for nicotine, as has d-amphetamine (Desai et al., 1999; Gasior et al., 1999; Mansbach et al., 1998). Some exceptions to this pattern of partial substitution have been noted. Cocaine did not substitute at all in squirrel monkeys trained to discriminate intravenous nicotine (Takada et al., 1988) and the dopamine uptake inhibitor bupropion fully substituted for the discriminative stimulus effects of nicotine in two studies (Wiley et al., 2002; Young and Glennon, 2002).

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Dopamine receptor antagonists produced mixed results. Flupenthixol blocked the discriminative stimulus effects of nicotine (Desai et al., 2003), although SCH23390 and haloperidol had no effect (Corrigall and Coen, 1994; Mansbach et al., 1998). In contrast, D2 and D3 agonists produced little or no nicotine-appropriate responding (Le Foll et al., 2005; Mansbach et al., 1998) and D2 and D3 antagonists did not block the discriminative stimulus effects of nicotine (Corrigall and Coen, 1994; Le Foll et al., 2005; Mansbach et al., 1998). These findings suggest that increasing levels of dopamine by dopamine releasers or uptake inhibitors may play some sort of role in the discriminative stimulus effects of nicotine, but that nicotine most likely does not act directly at dopamine receptors. This raises the question of how nicotine and methamphetamine might interact if the effects of methamphetamine are primarily dopamine mediated, whereas those of nicotine are primarily mediated by nicotinic acetylcholine receptors. The next section will review evidence for interactions of the behavioral effects of nicotine and methamphetamine as well as possible neural mechanisms for the interaction.

1.3. Interactions between Methamphetamine and Nicotine

Although nicotine and methamphetamine are often co-abused, few behavioral studies on the combination of nicotine and methamphetamine have been conducted. Those few studies have focused on modulation of locomotor activity and self-administration. Repeated administration of methamphetamine and nicotine produced sensitization to their effects in locomotor activity, and produced a symmetrical cross-sensitization in mice (Kuribara, 1999). Chronic treatment with nicotine for 14 days increased locomotor activity and stereotypy induced by methamphetamine (Suemaru et al., 1993). Nicotine attenuated reinstatement of methamphetamine self-administration (Hiranita et al., 2004; Hiranita et al., 2006), and mecamylamine decreased methamphetamine self-administration in rats (Glick et al., 2002). In rats trained to self-administer nicotine, bupropion and methamphetamine increased self-administration of low doses of nicotine and decreased self-administration of high doses of nicotine (Rauhut et al., 2003). These findings indicate a definite interaction between the two compounds; in particular, that the two compounds produce cross-sensitization implies a similar mechanism. The question then arises of what is the mechanism by which a nicotinic agonist and a dopamine releaser can interact. Because both locomotor activity and self-administration are known to be related to mesolimbic and nigrostriatal dopamine systems, it is possible that co-administration of these compounds modulates levels of DA release, particularly as nicotine is well known to modulate dopamine release (Quarta et al., 2006; Wonnacott et al., 2005)

There have indeed been reports that nicotine and methamphetamine modulate each other's ability to alter dopamine levels. Chronic treatment with nicotine increased release of dopamine in striatal slices (e.g., Takaki, 1995). In an *in vivo* microdialysis study in rats, nicotine did not alter dopamine levels in nucleus accumbens in naïve rats, but did increase dopamine levels in rats sensitized to nicotine. Methamphetamine produced smaller increases in dopamine levels in rats sensitized to nicotine, but basal levels of dopamine were higher to begin with (Miyata et al., 1996). Not only is there an interaction between presynaptic D2 and nicotinic acetylcholine receptors on their modulation of dopamine release, there is evidence that β2 subunits of the nicotinic acetylcholine receptors physically interact with the D2 receptors, creating a heteromeric receptor complex (Quarta et al., 2006). Taken together, these studies indicate that nicotine and methamphetamine can each modulate the other's behavioral effects and that there are known interactions between central dopamine and nicotinic acetylcholine receptors that could plausibly serve as mediators of interactions of the behavioral effects of methamphetamine and nicotine.

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1.4. Purpose of this study

The present study examined the effects of both nicotine and methamphetamine in rats trained to discriminate nicotine from saline or to discriminate methamphetamine from saline. First, the ability of methamphetamine to substitute in nicotine-trained rats and the ability of nicotine to substitute in methamphetamine-trained rats were tested. Then, the ability of a nicotinic (mecamylamine) and a dopaminergic (haloperidol) antagonist to block the discriminative stimulus effects of nicotine (in nicotine-trained rats) and methamphetamine (in methamphetamine-trained rats) was tested. Finally, the ability of the nicotinic and dopaminergic antagonists to block the ability of nicotine and methamphetamine to cross-substitute was tested. These experiments were conducted first to provide an assessment of the ability of nicotine and methamphetamine to modulate each other's discriminative stimulus effects. Such an assessment could provide a beginning for understanding why they are often co-abused. Secondly, the experiments provide an assessment of the pharmacological mechanism for the interaction.

2. Methods

2.1. Subjects

Male Sprague-Dawley rats were obtained from Harlan-Sprague Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 7:00 AM). Body weights were maintained at 320–350 g by limiting food to 20 g/day, which included the food received during operant sessions. Water was freely available. All housing and procedures were in accordance with the guidelines of the Institute of Laboratory Animal Resources, National Research Council (Institute of Laboratory Animal Resources, 1996) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

2.2. Discrimination training

Standard operant chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC compatible computers via LVB interfaces (Med Associates, East Fairfield, VT). The computers were programmed in MED-PC IV (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data.

Rats were trained to discriminate methamphetamine (1 mg/kg) or nicotine (0.4 mg/kg) from saline using a two-lever choice methodology. Food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer under a fixed ratio 10 schedule when responding occurred on the injection appropriate lever. There was no consequence for incorrect responses. The rats received approximately 60 training sessions before use in any behavioral experiment. Animals were selected for use in experiments when they had met the criteria of emitting 85% of responses on the injection-correct lever for both the first fixed-ratio and during the remainder of the session during their last 10 training sessions.

Training sessions occurred in a double alternating fashion (D-D-S-S-D, etc.), and tests were conducted between pairs of identical training sessions (i.e., between either two saline or two drug training sessions). Rats were tested only if they had achieved 85% drug-lever responding for both first fixed-ratio and total session on the two prior training sessions. Before each session, the rats received an injection of either saline or training drug. Ten minutes later, the rats were placed in an operant chamber. Each training session lasted a maximum of 10 min, and the rats could earn up to 20 food pellets.

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2.3. Test procedures

For all test sessions, intraperitoneal injections of the antagonists or their vehicle occurred 5 min prior to administration of nicotine or methamphetamine. Intraperitoneal injections of the training dose of methamphetamine occurred 10 min prior to the start of the test session, and subcutaneous injections of nicotine occurred 15 min prior to the start of the session. In contrast with training sessions, both levers were active, such that 10 consecutive responses on either lever led to reinforcement. Data were collected until the first reinforcer was obtained, or for a maximum of 20 min. At least three days elapsed between test sessions. Groups of 9 or 10 rats were tested with each test compound. A repeated measures design was used, such that each rat was tested at all doses in ascending order. Only data from the first reinforcer are depicted. Doses of the test compound for which fewer than four rats completed the first fixed ratio were not considered in the characterization of discriminative stimulus effects.

In nicotine-trained rats, nicotine (0.025 to 0.4 mg/kg) and methamphetamine (0.1 to 2.5 mg/kg) were tested for the ability to substitute for the discriminative stimulus effects of 0.4 mg/kg nicotine. In methamphetamine-trained rats, nicotine (0.05 to 1 mg/kg) and methamphetamine (0.1 to 1 mg/kg) were tested for the ability to substitute for the discriminative stimulus effects of 1 mg/kg methamphetamine. Mecamylamine (0.1–10 mg/kg, i.p.) or haloperidol (0.05–0.5 mg/kg, i.p.) were tested for their ability to antagonize the discriminative stimulus effects of the training dose of methamphetamine (1 mg/kg) or nicotine (0.4 mg/kg). For studies of the antagonism of cross-substitution, haloperidol (0.025 or 0.25 mg/kg) or mecamylamine (0.1 or 0.5 mg/kg) were tested with 0.25 mg/kg nicotine in methamphetamine-trained rats, and haloperidol (0.05 or 0.5 mg/kg) or mecamylamine (0.25, 1 or 10 mg/kg) were tested with 1 mg/kg methamphetamine in nicotine-trained rats.

2.4. Drugs

Nicotine ditartrate and mecamylamine hydrochloride were purchased from Sigma Chemical Co (St. Louis, MO). Haloperidol was donated by Janssen Pharmaceutica (New Brunswick, NJ). (+)-Methamphetamine hydrochloride was obtained from the National Institute on Drug Abuse. Haloperidol was dissolved in 0.16% tartaric acid in deionized water. All remaining drugs were dissolved in 0.9% saline. The pH of the nicotine solution was titrated to approximately neutral with small amounts of 0.1N sodium hydroxide. The doses of nicotine are expressed as weight of base. Nicotine was administered s.c. in a volume of 1 ml/kg, and all remaining drugs were administered i.p. in a volume of 1 ml/kg.

2.5. Data Analysis

Drug discrimination data were expressed as the mean percentage of responses made on the drug-appropriate lever prior to completion of the first fixed ratio. Percent drug-appropriate responding and response rate were plotted as a function of the dose of the test compound (log scale). Percent drug-appropriate responding was calculated for a given dose only if at least 3 rats completed the first fixed ratio. Full substitution was defined as ≥80% drug-appropriate responding, and partial substitution as ≥40% and <80% drug-appropriate responding. Full antagonism was defined as ≤20% drug-appropriate responding, and partial antagonism as ≤60% and >20% drug-appropriate responding. The potencies of nicotine and methamphetamine were calculated by fitting straight lines to the individual dose-response data for each compound by means of TableCurve 2D (Jandel Scientific, San Rafael, CA). Straight lines were fitted to the linear portion of dose-effect curves, defined by doses producing 20 to 80% of the maximal effect, including not more than one dose producing <20% of the maximal effect and not more than one dose producing >80% of the maximal effect. Other doses were excluded from the analyses. The slopes of the dose effect curves were compared using parallel line procedures (Kenakin, 1997). Comparison of the ED50 values was performed by two-way analysis of variance. Individual differences were compared using the Bonferroni-corrected post

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hoc test. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Response rate data was analyzed by one-way repeated measures analysis of variance. Effects of individual doses were compared to the appropriate control value using a priori contrasts. Criterion for significance was set a priori at $p<0.05$.

3. Results

3.1. Nicotine-trained rats

As shown in Figure 1 (left panels), nicotine (N=10) produced dose-dependent increases in nicotine-appropriate responding (ED_{50} = 0.059±0.008 mg/kg). Doses lower than the training dose of 0.4 mg/kg also produced full substitution (0.1 and 0.2 mg/kg). Nicotine produced an increase in response rate over that of the saline control at the 0.2 and 0.4 mg/kg doses [$F(5,45)=2.79$; $p=0.028$]. Methamphetamine (N=9) fully substituted for the training dose of nicotine (ED_{50} = 0.84±0.17 mg/kg). The full substitution was seen at a dose that produced depression of response rate [$F(5,40)=2.73$; $p=0.032$], and 3/9 rats failed to complete the first reinforcer.

Mecamylamine (N=10) fully antagonized the discriminative stimulus effects of nicotine (0.4 mg/kg), with the highest dose (0.5 mg/kg) reaching the 20% criterion for full antagonism (Fig. 1, right panels). Response rate was not affected [$F(3,27)=0.81$; $p=0.498$]. In contrast, haloperidol (N=10) failed to antagonize the discriminative stimulus effects of nicotine (0.4 mg/kg) and dose-dependently decreased response rates [$F(3,27)=3.93$; $p=0.019$]. Higher doses of haloperidol were not tested as they completely suppress response rates.

3.2. Methamphetamine-trained rats

As shown in Figure 2 (left panels), methamphetamine (N=10) produced a dose-dependent increase in methamphetamine-appropriate responding (ED_{50} = 0.35±0.07 mg/kg), but did not significantly alter response rates [$F(4,36)=1.48$; $p=0.228$]. In contrast, nicotine (N=12) only partially substituted, producing a plateau at 60 to 77% methamphetamine-appropriate responding (ED_{50} = 0.12±0.02 mg/kg). Higher doses were not tested because 1 mg/kg nicotine produced convulsions. The ED_{50} values for the experiments differed, such that nicotine was more potent than methamphetamine [$F(1,28)= 33.93$; $p<0.001$], and each compound was more potent when substituting for itself than when cross-substituting [$F(1,28)= 6.22$; $p=0.019$]. Nicotine produced a dose-dependent decrease in response rate [$F(5,55)=12.44$; $p<.001$].

Haloperidol (N=6) fully antagonized the discriminative stimulus effects of 1 mg/kg methamphetamine (AD_{50} = 0.13±0.02 mg/kg). In contrast, mecamylamine (N=10) produced very modest decreases in methamphetamine-appropriate responding (71 to 78%) which were not in the range for partial antagonism (Figure 2, right panels). Haloperidol did not alter response rate at the doses tested [$F(3,12)=0.57$, $p=0.644$]. Mecamylamine significantly decreased rates of responding at the highest dose tested to 44% of methamphetamine control [$F(7,63)=2.43$, $p=0.029$].

3.3. Antagonism of cross-substitution

3.3.1. Nicotine-trained rats—Haloperidol and mecamylamine in combination with the dose of methamphetamine that produced full substitution almost completely suppressed response rates (data not shown). For this reason, antagonism studies were conducted with 1.0 mg/kg methamphetamine (Figure 3, left panels). Methamphetamine (1 mg/kg) produced 65 ±15% nicotine-appropriate responding. Haloperidol (0.5 mg/kg) decreased nicotine-appropriate responding in the presence of 1 mg/kg methamphetamine to 37±13%. This was only a partial blockade (<60% and >20% nicotine-appropriate responding) of the ability of methamphetamine to substitute for nicotine. Haloperidol did not significantly alter response rates in comparison to methamphetamine control [$F(4,36)=2.01$; $p=0.088$]. The effects of

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mecamylamine (N=9) on methamphetamine substitution was not dose-dependent and nicotine-appropriate responding fluctuated between 56 and 80%. Mecamylamine did not depress response rates below that of methamphetamine alone [F(6,54)=1.36; p=0.246], although some rats did not complete the first fixed ratio at some doses (Figure 3).

Mecamylamine (10 mg/kg) when administered alone produced no nicotine-appropriate responding (3.0±3.0% DAR) and decreased response rate to 0.11±0.05 responses/s, which was significantly different from the saline control rate of 0.565±0.06 r/s [t=5.43, p<0.001]. Haloperidol (0.5 mg/kg) also produced no nicotine-appropriate responding (0%) when administered alone, and decreased response rate to 0.16±0.07 r/s, which was significantly different from the saline control rate of 0.42±0.07 r/s [t=2.66, p=0.008].

3.3.2. Methamphetamine-trained rats—As in the nicotine-trained rats, doses of haloperidol and mecamylamine in combination with nicotine (0.4 mg/kg) nearly completely suppressed response rates, so antagonism studies were conducted with 0.25 mg/kg nicotine. Nicotine (0.25 mg/kg) alone produced 74±11% methamphetamine-appropriate responding (Figure 2). Mecamylamine dose-dependently blocked the ability of nicotine to partially substitute for methamphetamine (12±8% following 0.5 mg/kg). In contrast, in a separate group of rats, haloperidol did not alter the level of methamphetamine-appropriate responding produced by 0.25 mg/kg nicotine at either dose (Figure 3). Mecamylamine also reversed the rate-decreasing effects of 0.25 mg/kg nicotine [F(2,18)= 7.98, *p*=0.003]. Haloperidol did not alter response rates [F(2,18)= 0.48, *p*=0.625].

Mecamylamine tested at doses from 0.1 to 10 mg/kg did not substitute for the discriminative stimulus effects of methamphetamine. Maximum methamphetamine-appropriate responding (35±16%) was observed following 10 mg/kg. Mecamylamine dose-dependently decreased response rates [F(7,63)=6.81, p<0.001]. The greatest effect (0.20±0.04 responses/s) was at 10 mg/kg, which was significantly different from the saline control rate of 0.49±0.08 r/s (p<0.05).

4. Discussion

4.1. Cross-substitution

In the present study, methamphetamine fully substituted for the discriminative stimulus effects of nicotine. This finding is in agreement with earlier findings that the dopamine uptake inhibitor bupropion also fully substituted for the discriminative stimulus effects of nicotine (Wiley et al., 2002; Young and Glennon, 2002), although other compounds that directly or indirectly activate dopamine receptors only produced partial substitution (Desai et al., 1999; Gasior et al., 1999; Mansbach et al., 1998). In contrast, nicotine only partially substituted for the discriminative stimulus effects of methamphetamine. It is significant to note that this finding was replicated in the present study by three separate groups of rats, one for the cross-substitution study and two for the antagonism experiments. In these experiments, nicotine produced 66 to 74% methamphetamine-appropriate responding. This observation has not been reported in the literature before. However, similar results have been reported for other psychostimulants. Nicotine fully substituted in rats trained to discriminate cocaine from saline (Desai et al., 1999; 2003), and potentiated the discriminative stimulus effects of d-amphetamine (Druhan et al., 1991), whereas monkeys and pigeons showed only partial substitution by nicotine (de la Garza and Johanson, 1983; 1985).

These findings suggest that there is an asymmetrical cross-substitution between methamphetamine and nicotine, such that administration of methamphetamine is sufficient to produce nicotine-like discriminative stimulus effects, whereas administration of nicotine is not sufficient to produce methamphetamine-like discriminative stimulus effects. The case for asymmetry should perhaps not be overstated, as earlier studies have reported both full and

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partial substitution by dopamine compounds in nicotine-trained subjects (Desai et al., 1999; Gasior et al., 1999; Mansbach et al., 1998) (Wiley et al., 2002; Young and Glennon, 2002) and both full and partial substitution by nicotine in other dopaminergic psychostimulants (de la Garza and Johanson, 1983; 1985; Desai et al., 1999; Desai et al., 2003). It is important to note that the degree of cross-substitution between methamphetamine and nicotine could be determined by training dose, as different patterns of stimulus control can be seen between groups trained to discriminate a high or a low dose of drug (Koek and Slangen, 1982; Stolerman et al., 1984). This effect is more pronounced when there are differences in mechanism or degree of efficacy between the compounds being tested, as is the case for methamphetamine and nicotine. That said, it is possible that methamphetamine is different from the other dopaminergic compounds and that the asymmetric cross-substitution is real. Alternatively, it is possible that the connection between nicotine and the dopaminergic compounds is of moderate strength, and that whether full or partial substitution is observed depends on individual differences among the subjects tested. Regardless of the degree, cross-substitution implies some sort of mechanistic connection between two compounds. The next section addresses possible mechanisms for the shared stimulus effects of nicotine and methamphetamine.

4.2. Mechanisms

In the present study, antagonism experiments were conducted to clarify the mechanism for the cross-substitution of nicotine and methamphetamine. Mecamylamine was used to probe for activity at central nicotinic acetylcholine receptors. Not surprisingly, mecamylamine blocked the discriminative stimulus effects of nicotine in the nicotine-trained rats, in agreement with earlier findings (Miyata et al., 1999; Rosecrans, 1989; Stolerman, 1988). Mecamylamine produced a small attenuation of the discriminative stimulus effects of methamphetamine in the methamphetamine-trained rats, but produced no effect on methamphetamine cross-substitution in the nicotine-trained rats. It should be noted that mecamylamine binds to NMDA receptors at concentrations higher than those necessary to produce nicotinic receptor mediated effects (Reynolds and Miller, 1988), and that NMDA antagonists facilitate the discriminative stimulus effects of methamphetamine (Gatch and Pratt, 2006). These findings indicate that nicotinic acetylcholine receptors do not contribute to the discriminative stimulus effects of methamphetamine as the small attenuation produced by large doses of mecamylamine in the present study were likely mediated by non-nicotinic receptors.

The non-selective dopamine antagonist haloperidol was used to test the contribution of dopamine receptors. Haloperidol blocked the discriminative stimulus effects of methamphetamine in methamphetamine-trained rats in agreement with earlier findings (Munzar and Goldberg, 2000; Tidey and Bergman, 1998). In contrast, the dopamine antagonist haloperidol did not alter the effects of nicotine in either the nicotine- or the methamphetamine-trained rats. These findings are not surprising given earlier studies that reported haloperidol had no effect on the discriminative stimulus effects of nicotine (Corrigall and Coen, 1994; Mansbach et al., 1998). What was unexpected was that haloperidol failed to fully antagonize the cross-substitution of methamphetamine in nicotine-trained rats. Haloperidol dose-dependently decreased nicotine-appropriate responding following methamphetamine from 65% to 37%. This is certainly not full antagonism of methamphetamine as seen with in the methamphetamine-trained rats. There are a number of possibilities of why haloperidol did not fully block the effects of methamphetamine in nicotine-trained rats. It is possible that haloperidol was less potent in the nicotine-trained rats, which may have resulted in the rate-decreasing effects preventing observation of full antagonism. Alternatively, the partial substitution of methamphetamine for nicotine may be mediated by more than just the dopamine system. Again, it should be noted that training dose could be an important factor in determining the degree of sensitivity of the assay, such that increased or decreased degrees of antagonism

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could be produced by altering training doses. Additional experimentation will be necessary to clarify why haloperidol had such a weak effect.

Taken together, these findings suggest that nicotine produced its discriminative stimulus effects in both the nicotine- and the methamphetamine-trained rats through its actions at central nicotinic acetylcholine receptors and not through any direct action at dopamine receptors. Likewise, methamphetamine produced its discriminative stimulus effects in both the nicotine- and the methamphetamine-trained rats through its effects on dopamine release, and that methamphetamine does not produce its discriminative stimulus effects through actions at central nicotinic acetylcholine receptors. What then mediates the interaction of nicotine and methamphetamine? The most obvious possibility is that nicotinic acetylcholine receptors are located on dopaminergic neurons in the ventral tegmental area which are important in regulating neuronal activity of these dopaminergic neurons (Mameli-Engvall et al., 2006; Ungless and Cragg, 2006). Administration of nicotine modulates dopamine release (Quarta et al., 2006; Wonnacott et al., 2005), and is known to alter behaviors controlled by these dopaminergic pathways including locomotor behavior (Kuribara, 1999; Suemaru et al., 1993) and self-administration of abused compounds, including both nicotine and methamphetamine (Glick et al., 2002; Hiranita et al., 2004; Hiranita et al., 2006; Rauhut et al., 2003). The failure of mecamylamine to block the cross-substitution of methamphetamine in nicotine-trained rats may be related to the finding that perfusion of mecamylamine into the nucleus accumbens did not alter dopamine levels in the ventral tegmental area or the nucleus accumbens (Rahman and McBride, 2002). In addition, there is now evidence that β2 subunits of nicotinic acetylcholine receptors create a heteromeric receptor complex with dopamine D2 receptors (Quarta et al., 2006). This hetereomeric autoreceptor decreases dopamine release, but as yet, the functional significance of this autoreceptor to dopamine-related behaviors has not been investigated. These findings do not confirm that alterations in dopamine levels in the mesocortical pathway mediates the behavioral interaction of nicotine and methamphetamine, but provides a plausible starting place for further research.

4.3. Conclusions

Typically, the effects of single drugs of abuse have been studied, even though they are rarely used singly. Nicotine is commonly used in combination with methamphetamine (Goldsamt et al., 2005; Yen and Chong, 2006), so there is a need for understanding the interactions between the two drugs of abuse. In the present study, nicotine and methamphetamine produced similar discriminative stimulus effects, such that methamphetamine fully substitutes for the discriminative stimulus effects of nicotine, and nicotine partially substitutes for the discriminative stimulus effects of methamphetamine. The mechanism for the cross-substitution between nicotine and methamphetamine is evidently some modulation of dopamine levels, directly by methamphetamine, or indirectly by nicotinic acetylcholine receptors in the case of nicotine. Given that both of these compounds modulate self-administration of the other compound (Glick et al., 2002; Hiranita et al., 2004; Hiranita et al., 2006; Rauhut et al., 2003), it is likely that people co-abuse nicotine and methamphetamine because of modulation of their stimulus and reinforcing effects, not just because both compounds are readily available in the same contexts. It is possible that people take the two compounds together because they modify the effects of each other to produce heightened effects or reduce unpleasant side-effects. Clearly, further clinical and mechanistic studies of the interaction of these two commonly abused substances is warranted.

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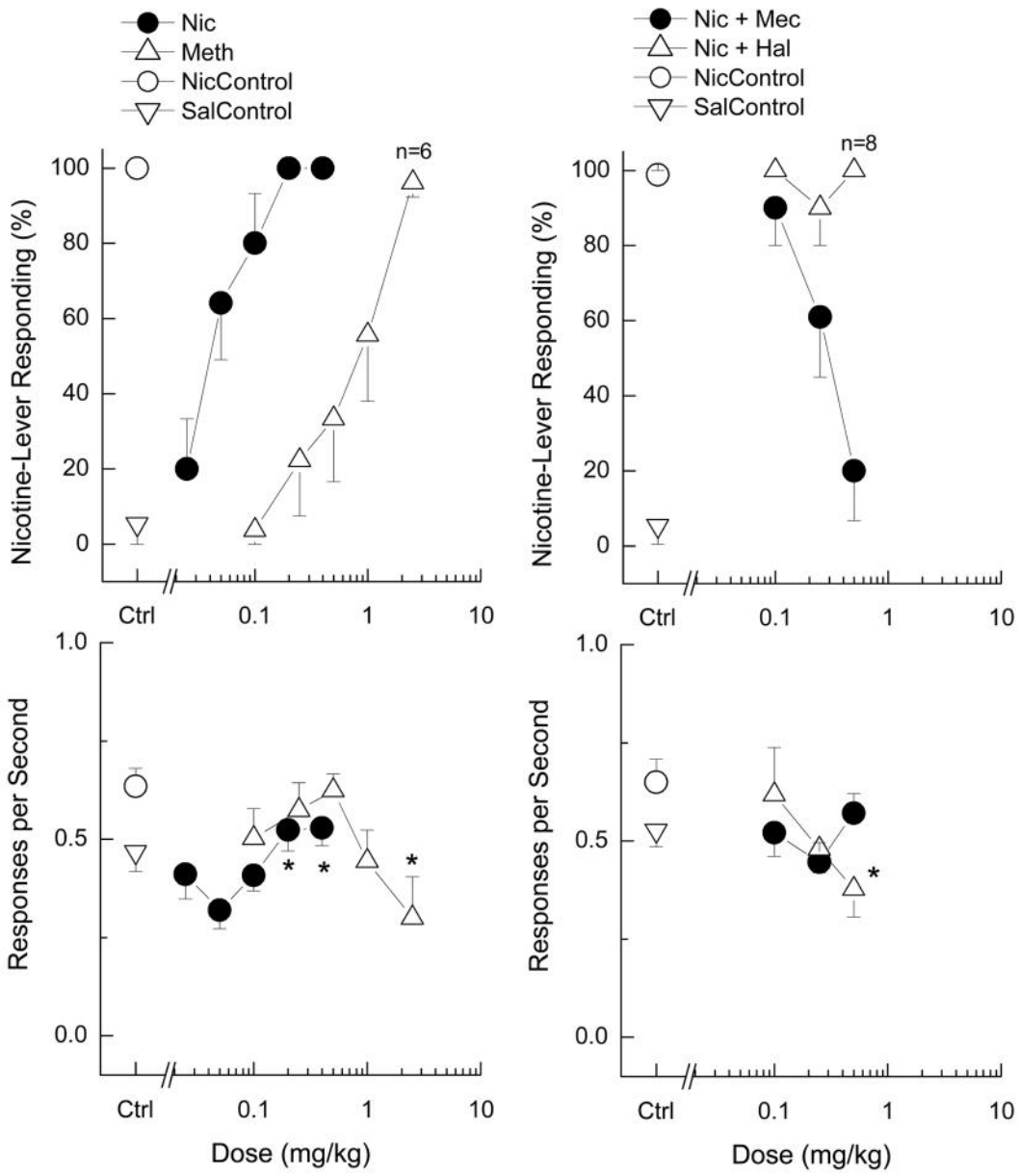

Figure 1. Substitution and blockade of the discriminative stimulus effects of nicotine (0.4 mg/kg, i.p.)

Top panels show percent nicotine-lever appropriate responding. Bottom panels show rate of responding (r/s). Nicotine and methamphetamine fully substituted for the discriminative stimulus effects of nicotine (left panels). Nicotine increased response rates, whereas methamphetamine decreased rates. Asterisks show response rates different from vehicle control ($p<0.05$). Mecamylamine fully blocked the discriminative stimulus effects of nicotine, whereas haloperidol had no effect (right panels). Mecamylamine did not change response rates, whereas haloperidol dose-dependently decreased rates. N=10 except where shown. Asterisks indicate response rates different from nicotine control ($p<0.05$). Nic=nicotine; Meth=methamphetamine. Hal= haloperidol; Mec=mecamylamine. Ctrl=control.

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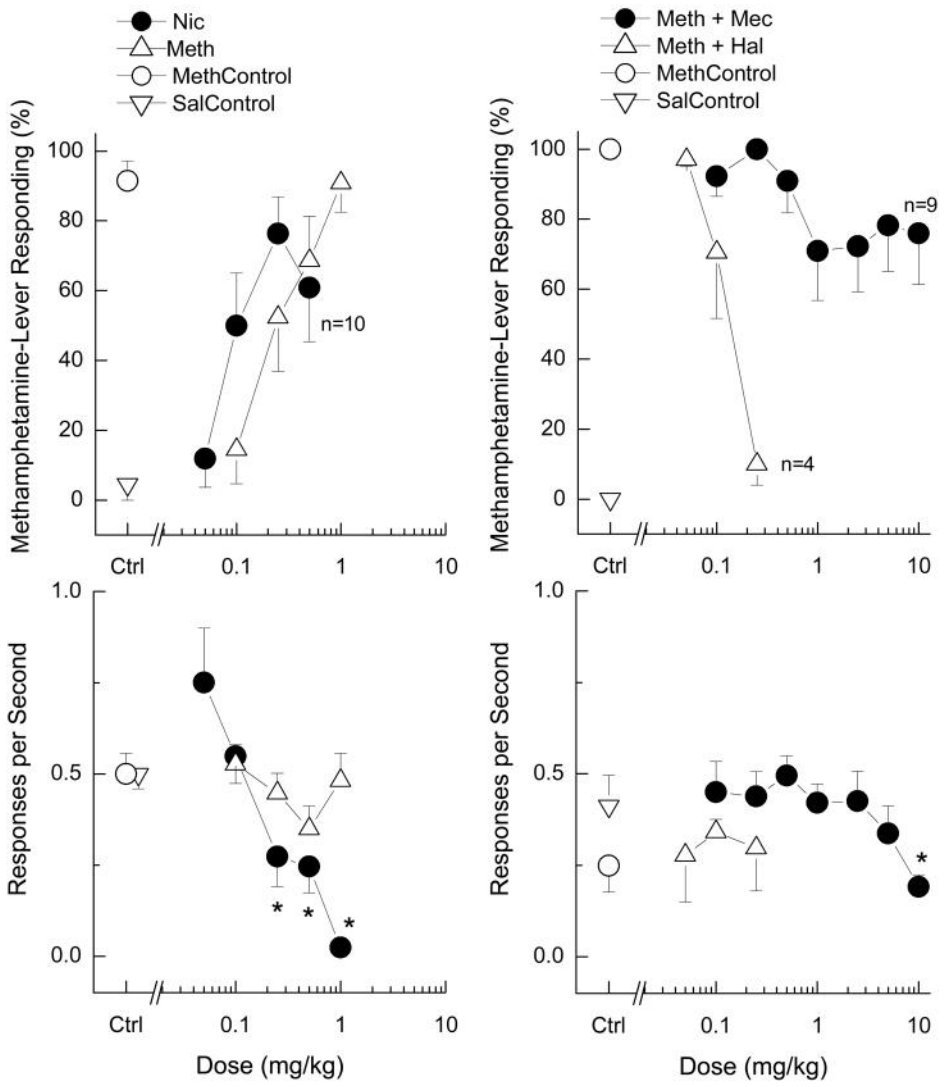

Figure 2. Substitution and blockade of the discriminative stimulus effects of methamphetamine (1 mg/kg, i.p.)

Top panels show percent methamphetamine-lever appropriate responding. Bottom panels show rate of responding (r/s). Methamphetamine fully substituted for the discriminative stimulus effects of methamphetamine, but nicotine produced only partial substitution (left panels). Methamphetamine did not alter response rates at the doses tested. Nicotine dose-dependently decreased response rates. Asterisks show response rates different from vehicle control ($p<0.05$). Haloperidol fully blocked the discriminative stimulus effects of methamphetamine, whereas mecamylamine produced only a small attenuation of drug-appropriate responding (right panels). Haloperidol did not change response rates, whereas mecamylamine decreased rates. N=10 except where shown. Asterisks indicate response rates different from nicotine control ($p<0.05$). Nic=nicotine; Meth=methamphetamine. Hal= haloperidol; Mec=mecamylamine. Ctrl=control.

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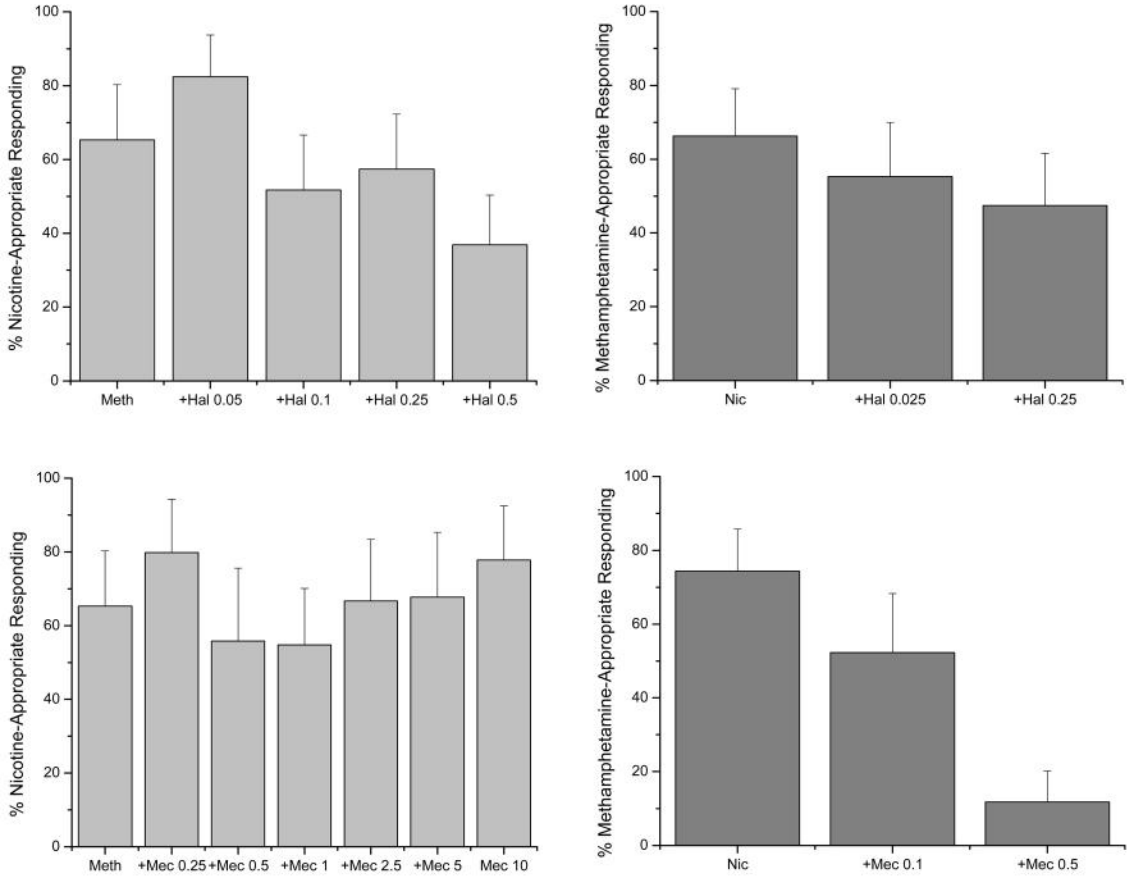

Figure 3. Antagonism of cross-substitution

Left panels show the effects of nicotine (0.25 mg/kg, s.c.) alone and in combination with mecamylamine and haloperidol in methamphetamine-trained rats. Nicotine partially substituted in methamphetamine-trained rats. The top panel shows haloperidol did not alter the effects of nicotine, whereas the bottom panel shows mecamylamine (0.1 and 0.5 mg/kg, i.p.) fully blocked the partial substitution of nicotine for methamphetamine. Right panels show the effects of methamphetamine (1 mg/kg, i.p.) alone and in combination with mecamylamine and haloperidol in nicotine-trained rats. The top panel shows haloperidol modestly attenuated the ability of methamphetamine to partially substitute for nicotine, whereas the bottom panel shows mecamylamine (0.25, 1 and 10 mg/kg, i.p.) did not alter the ability of methamphetamine to partially substitute for nicotine. Nic=nicotine; Meth=methamphetamine. Hal=haloperidol; Mec=mecamylamine.

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Methamphetamine: An Update on Epidemiology, Pharmacology, Clinical Phenomenology, and Treatment Literature

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Abstract

Background—Despite initial reports of a decline in use in the early 2000s, methamphetamine remains a significant public health concern with known neurotoxic and neurocognitive effects to the user. The goal of this review is to update the literature on methamphetamine use and addiction since its assent to peak popularity in 1990s.

Methods—Specifically, we first review recent epidemiological reports with a focus on methamphetamine accessibility, changes in use and disorder prevalence rates over time, and accurate estimates of the associated burden of care to the individual and society. Second, we review methamphetamine pharmacology literature with emphasis on the structural and functional neurotoxic effects associated with repeated use of the drug. Third, we briefly outline the findings on methamphetamine-related neurocognitive deficits as assessed via behavioral and neuroimaging paradigms. Lastly, we review the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial and pharmacological treatments within the context of an addiction biology framework.

Conclusion—Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Keywords

methamphetamine; stimulants; addiction; medication development

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1. Introduction

Methamphetamine use remains a significant public health concern in the United States (U.S.) and worldwide. Research has greatly advanced our knowledge of the epidemiology, consequences, and treatment of methamphetamine use disorders since methamphetamine's peak in popularity in the 1990s. Thus, the goal of this review is to update the literature on methamphetamine use and addiction since its assent to popularity. To do so, we cover recent epidemiological reports, methamphetamine pharmacology, and briefly outline the neurocognitive deficits associated with chronic methamphetamine use. We also discuss the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial interventions and pharmacological treatments.

This review is intended to supplement recent, more comprehensive reviews of pharmacologic treatments for methamphetamine addiction (i.e., Brackins et al., 2011; Brensilver et al., 2013; Rose and Grant, 2008) by distinguishing medications that have been tested clinically for reducing methamphetamine use from medications that may be promising based on their anti-craving effects – yet, clinical trials are ultimately needed. A number of other areas of potential interest to the field are also expanded upon, such as the trends in methamphetamine use/abuse rates, associated costs to the individual and society, and recent debates regarding methamphetamine-related neurocognitive impairments. Furthermore, the present review differs from other methamphetamine reviews (e.g., Panenka et al., 2013) by incorporating this wide range of domains of interest and by highlighting the increasingly recognized role for the opioidergic system in the development (i.e., reinforcement), maintenance (i.e., craving), and treatment (i.e., naltrexone) of methamphetamine addiction as an area for greater study in methamphetamine-related research. Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Articles for inclusion in this review were identified through an extensive literature search conducted in January, 2014 (and repeated in March, April, and July, 2014) in the PubMed and national survey databases. Search terms included "methamphetamine" (or "amphetamine" where appropriate) and domain specific terms such as "pharmacokinetics," "neurocognition," and "treatment." Efforts were made to include the most recent reports within each section in order to provide an updated summary of the current knowledge of the field.

1.1 Epidemiology of Methamphetamine

Methamphetamine remains a widely used illicit drug in the U.S. Estimates from 2012 suggest over 12 million people in the U.S., ages 12 years and older (4.7% of total responders) have used methamphetamine in their lifetimes, 1.2 million people (0.4 %) reported using methamphetamine in the past year, and approximately 440,000 (0.2%) of those identified as past month users (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013a). Amphetamine-type simulants (ATS), of which methamphetamine is the most frequently used, are the second most commonly used class of illicit drugs worldwide (United Nations Office on Drugs and Crime (UNODC), 2012); approximately 0.7 percent of the global population (33.8 million people) aged 15-64 years-

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old, reported using an ATS in 2010 (UNODC, 2013). Importantly, these estimates appear to be growing, as stated in the 2013 World Drug Report, "The market for ATS appears to be expanding in terms of locations of manufacture and trafficking routes, as well as in terms of demand" (UNODC, 2013).

1.2 History of Methamphetamine Use in the United States

ATS have a long history of use in the U.S., going as far back as World War II when soldiers used ATS to reduce fatigue and suppress appetite. ATS were widely prescribed in the 1950s and 1960s as a medication for depression and obesity, reaching a peak of 31 million prescriptions in the U.S. in 1967 (Anglin et al., 2000), with a roughly estimated 9.7 million Americans identified as past-year users of amphetamines in 1970 (Rasmussen, 2008). The rates of ATS use declined following the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970, which reclassified amphetamine to a more restrictive schedule, thereby limiting its accepted medical use (Gonzales et al., 2010). After amphetamine was rescheduled, illicit manufacturers began making methamphetamine using phenyl-2-propanone ("P2P") and methylamine. However, after P2P became a Schedule II controlled substance in 1980, ephedrine and pseudoephedrine became the predominant precursors and large quantities of these chemicals were smuggled from Mexico into the U.S. (Maxwell and Brecht, 2011). The increase in production was followed by a dramatic increase in use, with methamphetamine specifically increasing in popularity during the 1990s and early 2000s (Rawson et al., 2002). For example, estimates from the 2002 U.S. National Survey on Drug Use and Health (NSDUH) suggest that over 210,000 individuals ages 12 and older tried methamphetamine for the first time in 1991, whereas 454,000 individuals did so in 1998 (SAMHSA, 2003). Following the passage of the Combat Methamphetamine Epidemic Act in 2005 which restricted public access to products containing pseudoephedrine, the rates of methamphetamine use finally began to decrease (Gonzales et al., 2010; Maxwell and Brecht, 2011; Maxwell and Rutkowski, 2008), as evinced by a drop to 192,000 of new methamphetamine users in 2005 (SAMHSA, 2006).

This decline in methamphetamine use estimates was short lived however, as illicit manufacturers of methamphetamine began to use the P2P processes once again (Maxwell and Brecht, 2011). Estimates from the 2012 NSDUH identify over 130,000 individuals as new methamphetamine users in 2012, and the number of past month users in 2012 (440,000 people or 0.2%) remained consistent with reports from the last five years (0.1-0.2%) (SAMHSA, 2013a).

Recent reports of production and supply indicate a probable rise of methamphetamine use in the near future. For example, the number of methamphetamine laboratories reported in the U.S. quadrupled from 2,754 in 2010 to 11,116 in 2011, and the amount of methamphetamine seized by the U.S. government increased from 15 tons in 2010 to 23 tons in 2011 (UNODC, 2013). Furthermore, production methods are refined on an ongoing basis to produce purer and more potent forms of methamphetamine, and at lower costs. Analysis of data from the System to Retrieve Information on Drug Evidence (STRIDE), which reflects evidence submitted to DEA laboratories for analysis from July 2007 through September 2010, indicates that the price per pure gram of methamphetamine decreased 61%, from $270.10 to

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$105.49, while the purity increased 114%, from 39% to 83% (Maxwell and Brecht, 2011). Together, the culmination of recent prevalence, production, and supply data forewarn of an impending increase in methamphetamine use in the years to come.

1.3 Current Rates of Abuse and Dependence

Although the prevalence rates of current methamphetamine use have been relatively stable over the past five years, the rates of methamphetamine use disorders in the U.S. are on the rise. In 2012, 535,000 (0.2%) individuals were estimated to meet the Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM–IV; American Psychiatric Association, 1994) criteria of stimulant abuse or dependence, a significant increase from the 329,000 (0.1%) in 2011 (SAMHSA, 2013a). This increase was especially pronounced among individuals aged 18-25 years, with 0.5% meeting criteria in 2012, up from 0.3% in 2011. Over 379,000 of individuals were estimated to meet dependence criteria for methamphetamine in 2012, as compared to 252,000 in 2011 (SAMHSA, 2013a).

Estimates from the Treatment Episode Data Set (TEDS), which provides information on admissions to substance abuse treatment facilities that are licensed or certified by state substance abuse agencies, suggest that treatment admissions for primary methamphetamine increased from 78,248 individuals ages 12 or older (4.4% of admissions) in 2001 to 154,364 individuals (8.1%) in 2005, but then decreased to 102,384 individuals (5.6%) in 2011 (SAMHSA, 2013b). The recently released TEDS data report a slight increase for 2012, with 116, 090 individuals (6.6%) being admitted for primary methamphetamine-related problems (SAMHSA, 2014).The rates of methamphetamine dependence appear to be roughly equivalent in men compared to women, with 53% of primary methamphetamine/amphetamine admissions being male. Further, the majority of individuals admitted to treatment were non-Hispanic White (69%), followed by individuals of Mexican origin (12%; SAMHSA, 2014). Thus, methamphetamine dependence is largely a disorder of the White population; however, this may be a byproduct of the regional variability in methamphetamine use, which is currently greatest in the West and parts of the Midwest (NIDA, 2012).

1.4 Burden of Care Associated with Methamphetamine Use

In 2009, the RAND Corporation published the first national estimate of the economic burden of methamphetamine use based on information available for 2005 (Nicosia et al., 2009). They estimated the economic burden of methamphetamine use in the U.S. to be approximately $23.4 billion, which includes the costs associated with drug treatment, other health costs, the intangible burden of addiction and premature death, lost productivity, crime and criminal justice costs, child endangerment, and harms resulting from production. These intangible costs of addiction make up a substantial portion of the overall cost, at approximately $12.6 billion; which includes the costs associated with drug treatment at approximately $545 million, primarily delivered in the community-based specialty treatment sector ($491 million; Nicosia et al., 2009). These high costs are consistent with the TEDS data, which indicate that primary methamphetamine/amphetamine admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/residential treatment (16 % vs. 7 %) (SAMHSA, 2013b).

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In summary, methamphetamine use and the associated disorders constitute a significant burden to the individual and to society. Furthermore, the substantial time and resources devoted to the treatment of methamphetamine use disorders in the U.S. underscores the need for more efficacious, cost effective, and easily deliverable treatments.

2. Pharmacology of Methamphetamine

2.1 Chemistry of Methamphetamine

Methamphetamine, also known as metamfetamine, N-methylamphetamine, methylamphetamine, and desoxyephedrine, is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs. Methamphetamine exists in two stereoisomers, the l and d- forms. D-methamphetamine, or the dextrorotary enantiomer, is a more powerful psychostimulant, with 3-5 times the central nervous system (CNS) activity as compared to l-methamphetamine, or the levoratary enantiomer (Ciccarone, 2011); however, both enantiomers influence dopamine release and can induce stereotypy (i.e., persistent mechanical repetition of speech or movement) and psychosis at high doses (Kuczenski et al., 1995). Illicitly, methamphetamine may be sold as pure d-methamphetamine (dextromethamphetamine) or in a racemic mixture, and presents as powder or crystalline form, the latter commonly referred to as "ice" or "crystal meth" (Cruickshank and Dyer, 2009). Crystalline methamphetamine typically refers to a highly purified form of d-methamphetamine which is intended for smoking, with similar effects to that from an intravenous dose (Cho, 1990). Further, crystalline methamphetamine is associated with an increased incidence of dependence, as compared to the lower purity forms (McKetin et al., 2006).

2.2 Molecular Pharmacology of Methamphetamine

Methamphetamine is a cationic lipophilic molecule which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho and Melega, 2002). Due to its structural similarity, methamphetamine substitutes for the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulate postsynaptic monoamine receptors (Cruickshank and Dyer, 2009). Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase (Sulzer et al., 2005), further enabling the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of methamphetamine act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008). The medial basal forebrain, the hippocampus, and the prefrontal cortex (PFC) represent noradrenergic regions of interest, with various functions related to arousal, memory consolidation, and cognitive

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processing, respectively (Berridge and Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). However, the wide distribution of monoamines throughout the CNS, interactions between the monoamine pathways, baseline dopamine (and likely other monoamine) functioning, and peripherally mediated effects of methamphetamine add to the complexity of methamphetamine's effect on the monoamine systems (Cruickshank and Dyer, 2009).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid systems in the establishment of reinforcement (Boutrel, 2008). Three families of endogenous opioid peptides have been identified (dynorphins, endorphins and enkephalins), each associated with a distinct polypeptide precursor (prodynorphin, proopiomelanocortin, and proenkephalin). These precursors produce a number of active ligands including β-endorphin, met- and leu-enkephalin, dynorphins, and neo-endorphins (Kieffer and Gavériaux-Ruff, 2002). Each ligand expresses a different affinity for each opioid receptor; for example, β-Endorphin binds with higher affinity to μ- than δ- or κ-opioid receptors (Mansour et al., 1995b).

Anatomically speaking, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc; Mansour et al., 1995a).

Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ- and δ-opioid receptors in the NAcc (Hirose et al., 2005; Murakawa et al., 2004), and by decreasing GABA-inhibition via μ- and κ-opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci and Williams, 1997; Shoji et al., 1999). Many non-opioid drugs of abuse are also known to interact with the endogenous opioid system (for a review see Trigo et al., 2010). For example, preclinical studies in rats have shown that ethanol, cocaine, and d-amphetamine increase extracellular levels of endorphins in the NAcc (Olive et al., 2001), and that ethanol-induced increases in extracellular levels of dopamine in the NAcc are modulated by endogenous opioid system processes (e.g., Acquas et al., 1993; Lee et al., 2005). In humans, the rewarding effects of alcohol have been shown to be mediated by alcohol-induced endogenous opioid release in the NAcc and orbitofrontal cortex (OFC; Mitchell et al., 2012). Further, tobacco use, nicotine dependence severity, and nicotine craving were associated with reduced binding potential of a μ-opioid receptor agonist ([^{11}C]-carfentanil) in a number of mesolimbic regions in an alcohol dependent sample (Weerts et al., 2012). Together, these reports are suggestive of a general mediating role for the endogenous opioid system in the rewarding properties of multiple drugs of abuse.

ATSs have also been shown to affect the endogenous opioid system, which may mediate some of the rewarding properties associated with acute ATS use (Boutrel, 2008). For example, acute amphetamine administration has been linked with increased β-endorphin levels in the nucleus accumbens (Olive et al., 2001), increased striato-nigral dynorphin-like

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immunoreactivity (Bustamante et al., 2002; Hanson et al., 1988), and changes in the endogenous opioid mRNA expression in the striatum (Hurd and Herkenham, 1992; Smith and McGinty, 1994; Wang and McGinty, 1995). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of methamphetamine-induced behavioral (locomotor) sensitization (Chiu et al., 2006), analogous to compulsive drug seeking behavior in humans (i.e., drug craving; Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford et al., 2006).

In sum, methamphetamine has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

2.3 Clinical Pharmacokinetics of Methamphetamine

Methamphetamine is largely metabolized in the liver, resulting in metabolites including amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, and 4-hydroxynorephedrine (Caldwell et al., 1972). It is then excreted by the kidneys, with the majority excreted as unchanged methamphetamine (30-50%), followed by up to 15% as 4-hydroxymethamphetamine, and 10% as amphetamine. Approximately 70% of a single oral dose is excreted in the urine within 24 hours (Cook et al., 1993; Kim et al., 2004). With repeated dosing, methamphetamine can accumulate in the urine, with one study showing detection 7 days after a regimen of four daily 10mg oral doses (Oyler et al., 2002). Based on the pharmacokinetic data reviewed below, the typical assessment of methamphetamine abstinence in clinical studies consists of urinalysis at 3-4 day intervals (i.e., twice weekly).

Methamphetamine is commonly smoked, injected, ingested, snorted, dissolved sublingually, taken rectally, or solubilized and consumed as a liquid. Smoking, the most common route of administration (NIDA, 2012), and intravenous injection result in the near-immediate euphoric sensation which typically lasts for several minutes, as opposed to intranasal and oral injection which take approximately 5 and 20 minutes to reach peak euphoric state. The "high" through intranasal and oral methods however, is reported to last 8 to 12 hours (Meredith et al., 2005). When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion (Caldwell et al., 1972).

2.4 Clinical Response and Withdrawal of Methamphetamine

Methamphetamine is a potent CNS stimulator. As such, the clinical response to methamphetamine administration at low to moderate doses (5–30mg) includes euphoria, arousal, reduced fatigue, euphoria, positive mood, tachycardia, hypertension, pupil dilation, peripheral hyperthermia, reduced appetite, behavioral disinhibition, short-term improvement in cognitive domains, and anxiety (for a review see Cruickshank and Dyer, 2009). At frequent and high doses, there is also evidence that methamphetamine can induce psychotic episodes (Hermens et al., 2009; Ujike and Sato, 2004).

Frequent use of methamphetamine results in a depletion of presynaptic monoamine stores, down-regulation of receptors, and neurotoxicity (Barr et al., 2006; Meredith et al., 2005),

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resulting in significant psychiatric withdrawal symptoms following abrupt cessation after periods of regular use. Symptoms of methamphetamine withdrawal include anhedonia, hypersomnia, irritability, anxiety, aggression, and intense cravings for methamphetamine (Cantwell and McBride, 1998; Meredith et al., 2005). Depressive symptomatology has been considered the hallmark of methamphetamine withdrawal, with depressive symptoms lasting beyond two weeks of abstinence (Zorick et al., 2010). The severity of the withdrawal syndrome appears to be related to the frequency of use, yet methamphetamine withdrawal largely resolves spontaneously (Newton et al., 2004), and usually within 14 days of abstinence (Zorick et al., 2010). Protracted withdrawal from methamphetamine may in turn take several weeks to resolve and poses a large obstacle to sustained recovery.

2.5 Neurotoxicity Associated with Chronic Methamphetamine Use

Repeated exposure to moderate to high levels of methamphetamine has been related to neurotoxic effects on the dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies (Cho and Melega, 2002). Although the precise mechanisms remain unclear, the culmination of evidence suggests that the high level of cytoplasmic dopamine released as a result of methamphetamine use leads to the accumulation of reactive oxygen species and severe oxidative stress on the neuron (Berman et al., 2008a). Results of non-human primates given doses of methamphetamine roughly equivalent to a typical human abuse pattern of use (0.5-2mg/kg given four times at 2-hour intervals), indicate that methamphetamine at this (typical) level of use produces long-term reductions in dopaminergic axonal markers in the brain, including decreased striatal DAT density (Villemagne et al., 1998). Human studies using positron emission tomography (PET) and magnetic resonance imaging (MRI) data also provide support for prolonged neurotoxicity following repeated methamphetamine use. Reductions in striatal DAT site density (McCann et al., 1998; Volkow et al., 2001b, 2001d), D2 receptor availability (Volkow et al., 2001a), VMAT-2 density (Johanson et al., 2006), and SERT density (Sekine et al., 2006), have all been reported, with some markers (i.e., DAT density) showing improvement following prolonged (greater than 12 months) abstinence (Volkow et al., 2001b). Neurotoxic effects have been associated with behavioral and cognitive changes, such as memory deficits and impaired psychomotor coordination associated with reduced DAT site density (Volkow et al., 2001d), and increased aggression associated with reduced SERT density (Sekine et al., 2006). Chronic abuse of methamphetamine is also associated with reduced markers of neuronal integrity and increased markers of glial content, possibly indicating the proliferation of glial cells following neural damage (Chang et al., 2007; Ernst et al., 2000).

Structural brain abnormalities among frequent methamphetamine users as compared to healthy controls have also been observed, including, but not limited to, reduced white-matter integrity and/or organization associated with depression severity and positive psychiatric symptoms (Tobias et al., 2010), reduced gray matter in the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004), reduced hippocampal volumes associated with poorer memory performance (Thompson et al., 2004), altered shape of the corpus callosum (Oh et al., 2005), and increased volumes of the putamen and globus pallidus (interpreted as a compensatory effect; Chang et al., 2005). As noted by Berman and colleagues (2008a),

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lower cortical gray matter density or volume is the most consistently reported structural abnormality in amphetamine users, and studies assessing striatal gray matter report larger volumes in amphetamine abusers when compared to healthy controls, although the latter may reflect a compensatory response to initial neurotoxicity (Berman et al., 2008a).

A number of functional brain abnormalities have been observed in recently abstinent chronic abusers of methamphetamine. Using glucose metabolism as a marker of functional activity, regions of abnormally high relative activity include the amygdala, ventral striatum, and lateral orbitofrontal cortex (OFC), whereas abnormally low activity was observed in the medial PFC and cingulate cortex (London et al., 2004). Furthermore, glucose metabolism in the anterior and middle cingulate gyrus and the insula was negatively correlated with error rates on an auditory vigilance task in recently abstinent (4 to 7 days) methamphetamine abusers (London et al., 2005). Relative higher global and parietal cortex glucose metabolism has been noted to accompany continued abstinence (Berman et al., 2008b; Volkow et al., 2001c), along with relatively lower metabolism in striatal and thalamic regions (Volkow et al., 2001c; Wang et al., 2004). Importantly, some degree of recovery has been observed in the neocortical regions (Berman et al., 2008b) and thalamus (Wang et al., 2004) following one and nine months of abstinence, respectively.

3. Neurocognitive Functioning Associated with Chronic Methamphetamine Use

Chronic methamphetamine use has been associated with discrepancies in numerous cognitive processes dependent upon fronto-striatal and limbic circuits. However, differentiating preexisting deficits from methamphetamine-induced cognitive deficits poses significant challenges (Dean et al., 2013), and concerns regarding the interpretation of these discrepancies and their clinical significance have been raised (Hart et al., 2012). Despite this, the preponderance of evidence from preclinical, cross-sectional human, and brain imaging studies supports the assertion that methamphetamine abuse does indeed cause cognitive decline in at least some individuals (i.e., individuals at the age of early-to-middle adulthood; Dean et al., 2013) and that some cognitive/behavioral changes may be the result of methamphetamine neurotoxicity (Bortolato et al., 2009). Further, individual difference variables such as age, education level, and genotype appear to moderate the relationship between methamphetamine use and cognitive deficits (Dean et al., 2013).

With respect to the specific cognitive domains potentially affected, a meta-analysis of 18 studies found medium effects of methamphetamine use disorders on processes including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions. Small, yet significant, effects were also observed on measures of attention/working memory, language, and visuoconstruction (Scott et al., 2007).

A small number of these cognitive processes have been further examined using functional neuroimaging procedures in chronic methamphetamine users (for a review see Aron and Paulus, 2007). For example, the brain correlates of learning and cognitive control in methamphetamine abusers have been investigated using a color-word Stroop task

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administered during functional magnetic resonance imaging (fMRI). On this task, methamphetamine abusers display reduced reaction-time (RT) adjustments and reduced PFC activity following conflict (i.e., incongruent) trials (Salo et al., 2013, 2009), and reduced RT, increased error rate, and reduced activation of the right inferior frontal gyrus (IFG), supplementary motor cortex/anterior cingulate gyrus, and the anterior insular cortex during the incongruent condition (Nestor et al., 2011). Using a reversal learning task and PET in a preclinical sample, vervet monkeys given a chronic, escalating-dose regimen of methamphetamine revealed associations between the change in response to positive feedback and individual differences in the change in dopamine D_2-like receptor availability in the striatum, assessed pre- and post-methamphetamine regimen (Groman et al., 2012); thus advancing D_2 specific alterations of the dopaminergic system as a plausible neurobiological pathway subserving some of the disturbances in learning observed with repeated methamphetamine use.

Methamphetamine use disorders are associated with differential brain activity during decision-making, as assessed via fMRI. Methamphetamine abusers displayed reduced activation in the right IFG and the left medial frontal gyrus during a two-choice prediction task (where only 50% of the responses are reinforced with a correct response outcome), and a decrease in dorsolateral PFC (dlPFC) and right OFC activity in the active compared to control conditions, as opposed to the increase of activation in these areas observed in the healthy controls (Paulus et al., 2002). In a follow-up study using the same task, recently abstinent (average 25 days) individuals with methamphetamine dependence displayed reduced activation of the OFC, dlPFC, anterior cingulate cortex (ACC), and parietal cortex irrespective of the outcome, and attenuation of specific "success-related" patterns of brain activation as compared to healthy controls (Paulus et al., 2003). Furthermore, the degree of activation in the right middle frontal gyrus, middle temporal gyrus, and posterior cingulate during the two-choice prediction task in early remission (3-4 weeks abstinent) was predictive of relapse during a one-year follow-up (Paulus et al., 2005).

Methamphetamine dependence has also been associated with maladaptive reward-related decision-making, as indexed via steeper rates of temporal discounting ("delay discounting") (Hoffman et al., 2006). Contrasting "hard choices", where roughly equivalent preference is obtained for the immediate and delayed reward choices, and "easy choices", in which the choices differ dramatically in value and preference, revealed less activation in the precuneus, right caudate nucleus, ACC, and dlPFC in recently abstinent (2-8 weeks) individuals with methamphetamine dependence (Hoffman et al., 2008), and less activation of the left dlPFC and right intraparietal sulcus in active methamphetamine abusers (Monterosso et al., 2007), as compared to healthy controls. Furthermore, methamphetamine dependent individuals undergoing treatment display disrupted risk-related processing, a component of decision-making, on the Risky Gains Task in both the ACC and insula (Gowin et al., 2013).

In summary, methamphetamine use disorders are associated with specific task-related behavioral and neural processing differences across a number of cognitive domains, which appear to be moderated by individual difference variables. Importantly, evidence is accumulating to suggest some of these differences are associated with altered dopaminergic

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processing (Groman et al., 2012) and clinically meaningful outcomes (Paulus et al., 2005), suggestive of a functional role for these cognitive differences in the development and perpetuation of methamphetamine addiction.

4. Clinical Presentation of Methamphetamine Use Disorders

A methamphetamine use disorder represents a complex psychiatric condition characterized by a set of maladaptive behaviors which result in clinically significant functional impairment (American Psychiatric Association, 1994, 2013). A diagnosis made using the DSM-IV criteria necessitates the experience of at least 1 symptom of abuse or 3 symptoms of dependence occurring within a 12-month period (American Psychiatric Association, 1994), whereas the fifth edition of the DSM (DSM-5) combines these criterion (with a few notable changes) to form a single "methamphetamine use disorder" with an added severity specification (American Psychiatric Association, 2013). The DSM-specified criteria include maladaptive behaviors such as "continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of methamphetamine", the development of "tolerance" and "withdrawal," and "persistent desire or unsuccessful efforts to stop or cut down or control methamphetamine use."

The two most notable changes to the DSM-5 criteria include the removal of "legal problems" and the addition of "drug craving" to the symptom list. The addition of "craving" as a possible symptom represents an effort to increase consistency between DSM-5 and the International Classification of Diseases (ICD-10; World Health Orgainization, 2010), as well as acknowledgment of a vast amount of scientific research highlighting the importance of craving for understanding the pathogenesis and maintenance of addiction (e.g., Robinson and Berridge, 1993, 2001). Specific to methamphetamine addiction, research suggests individuals with this disorder exhibit cognitive performance deficits that are more pronounced during exposure to methamphetamine-related cues (Tolliver et al., 2012), and that level of craving for methamphetamine is associated with neural and behavioral measures of self-control (Tabibnia et al., 2011), together suggestive of a strong neural relationship between craving and clinically relevant behavioral markers of addiction. Furthermore, methamphetamine craving has been observed to be present for at least 5 weeks into abstinence, rendering the user particularly vulnerable to relapse during 7 to 14 days of abstinence (Zorick et al., 2010), and is a significant predictor of subsequent use during outpatient treatment (Galloway and Singleton, 2009; Hartz et al., 2001). Craving beliefs, or interpretations and decisions about cravings, have also been shown to predict relapse in a sample of regular methamphetamine users (Lee et al., 2010). On this basis, methamphetamine craving has been advanced as a surrogate marker of methamphetamine dependence (Galloway and Singleton, 2009). As with other substance use disorders, methamphetamine addiction is considered a chronic and relapsing disorder characterized by neurobiological changes that subserve the observed functional impairment in the individual (Koob et al., 2004).

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5. Treatment of Methamphetamine Use Disorders

At present, few effective options exist for individuals seeking treatment for methamphetamine use disorder, and to date these options have been limited to psychosocial interventions. Twelve-Step programs, such as Narcotics Anonymous, remain a common intervention pursued by many individuals with methamphetamine use concerns (Galanter et al., 2013) despite a lack of evidence supporting the efficacy of these programs as a stand-alone treatment (Donovan and Wells, 2007; Shearer, 2007). There is some, albeit modest, evidence to suggest that other psychological interventions are effective for stimulant users (Knapp et al., 2007; Shearer, 2007; Vocci and Montoya, 2009). However, the majority of the treatment efficacy research has been done with cocaine abusing populations, and given the known differences between individuals seeking treatment for methamphetamine versus cocaine (i.e., age of first use, route of administration, frequency of use, demographics, and prior exposure to treatment; Huber et al., 1997), it remains unclear whether the efficacy of these interventions is generalizable to individuals with a methamphetamine use disorder.

5.1 Psychosocial Treatments

A systematic review of cognitive and behavioral treatments as applied specifically to methamphetamine use disorders concluded that good clinical outcomes are achieved with Cognitive-Behavioral Treatment (CBT; with and without Motivational Interviewing [MI]) and Contingency Management (CM) therapies involving the systematic use of reinforcement (Lee and Rawson, 2008). A number of caveats must be considered when interpreting these conclusions however, such as the durability of treatment effects (especially with respect to CM programs). Furthermore, the effectiveness of psychosocial interventions is compromised by poor rates of treatment induction and retention (Shearer, 2007), and methamphetamine-related cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments ineffective (Baicy and London, 2007).

5.2 Pharmacologic Treatments

Given these important caveats of psychosocial interventions, and the heavy focus on the neurobiology of methamphetamine dependence, attention has shifted to the development of efficacious pharmacotherapies for methamphetamine addiction (NIDA, 2005). At present, no medication is approved by the U.S. Food and Drug Administration (FDA) for use in methamphetamine dependence. Numerous classes of medication are currently under study, primarily in small clinical trials (for a recent focused review see Brensilver et al., 2013). Medications presumed to have potential for the treatment of methamphetamine addiction frequently target dopaminergic, serotonergic, GABAergic, and/or glutamatergic brain pathways (for a review see Vocci and Appel, 2007), as well as opioidergic pathways (e.g., Brensilver et al., 2013). Additionally, cognitive enhancing medications such as modafinil (an analeptic drug with known cognitive-enhancing properties) have garnered attention given the known cognitive deficits associated with chronic methamphetamine use (e.g., Ghahremani et al., 2011).

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5.2.1 Medications associated with reduced methamphetamine use—A focused review on pharmacological treatments for methamphetamine/amphetamine dependence identified only three double-blind placebo-controlled trials that have shown positive results for reducing use of the substance (Karila et al., 2010). The first two trials found treatment effects within a specific subpopulation of users; namely buproprion was associated with a reduction of methamphetamine use among baseline light, but not heavy, methamphetamine users (identified in a posthoc analysis; Shoptaw et al., 2008), and modafinil combined with CBT was associated with reduced methamphetamine use within a small sample of HIV+ gay men dependent on methamphetamine (McElhiney et al., 2009), although recent trials have not found strong support for a direct effect of modafinil on abstinence outcomes (e.g., Anderson et al., 2012; Heinzerling et al., 2010). The third trial found support for reduced amphetamine use and greater abstinence rates with naltrexone treatment (50mg) in a sample of amphetamine-dependent individuals (Jayaram-Lindstrom et al., 2008).

Since the review, a few medications have received support for reducing methamphetamine use, namely mirtazapine, topiramate, and naltrexone. Specifically, 12-weeks of mirtazapine treatment combined with CBT/MI counseling was associated with significant reductions in methamphetamine use (percent positive urines at the week 12 visit) in a sample of methamphetamine-dependent men who have sex with men (MSM) (Colfax et al., 2011).

Topiramate was associated with more patients achieving a 50 or 25 percent reduction in baseline level of methamphetamine use in large multi-site clinical trial; however, no effects on total abstinence (negative urines during 6-12 week follow-up) were observed (Elkashef et al., 2012). Further analysis of this data identified a small subgroup of patients who exhibited consistent reductions or achieved abstinence during follow-up, which were associated with topiramate treatment. This subgroup consisted of individuals who were more likely to have discontinued methamphetamine use (i.e., have a negative last urine) during the week prior to randomization (Ma et al., 2013), suggesting that topiramate may function best for relapse prevention. An additional study has found support for of the use of implant naltrexone for the treatment of problematic amphetamine use, noting patients with high levels of naltrexone (≥2 ng/ml) in their blood were 2.27 times more likely to be abstinent than patients with low naltrexone blood levels (<2 ng/ml; Grant et al., 2010). Clinical and preclinical laboratory models have also found support for reduced ATS use with naltrexone treatment. Specifically, clinical laboratory studies of naltrexone found reductions of both heroin and amphetamine use in a sample of individuals dependent on both substances (Tiihonen et al., 2012), and decreases in quality/liking ratings of administered amphetamine in a sample comprised of predominant cocaine users (Comer et al., 2013). Preclinical studies have observed naltrexone-related decreases in d-amphetamine and alcohol self-administration in adult rhesus monkeys (Jimenez-Gomez et al., 2011), and attenuated amphetamine-induced reinstatement with no effect on food taking behavior in the rat (Haggkvist et al., 2009).

The potential efficacy of naltrexone, an opioid antagonist with greatest affinity for the μ-opioid receptor and to a lesser but meaningful extent κ-and δ-opioid receptors (Ashenhurst et al., 2012), may lie in its ability to block drug-induced β-endorphin, and subsequent dopamine, release in the NAcc and through the blockade of drug-induced β-endorphin inhibition of GABAergic inhibitory interneurons in the VTA, as in the case of alcohol

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(Johnson, 2008; Zalewska-Kaszubska et al., 2006). The decrease in amphetamine-induced dopamine levels in the NAcc following blockade of the μ-opioid receptor by naltrindole (a selective 8-opioid receptor antagonist) and β-funaltrexamine (an irreversible μ-opioid receptor antagonist) provides support for this hypothesis (Schad et al., 1996). However, the efficacy of naltrexone treatment for methamphetamine dependent individuals remains unclear.

5.2.2 Medications associated with reduced methamphetamine craving—Given the putative role of craving in the maintenance of addiction, numerous medications have also been tested for their ability to alleviate methamphetamine craving. These medications include ondansetron (Johnson et al., 2008), methylphenidate (Miles et al., 2013), a combination of flumazenil, gabapentin and hydroxyzine (Ling et al., 2012), modafinil (Shearer et al., 2009), topiramate (Johnson et al., 2007), aripiprazole (Newton et al., 2008), sertraline (Zorick et al., 2011), and isradipine (Johnson et al., 2005). Unfortunately, none of these medications have shown associated reductions in subjective methamphetamine craving, and two of these medications, namely aripiprazole and sertraline, have even been associated with increased (Newton et al., 2008) or sustained (Zorick et al., 2011) craving following treatment, respectively.

Nevertheless, a few medications have shown potential to reduce methamphetamine craving. Treatment with dextroamphetamine, as a potential substitution therapy, has been shown to reduce craving, but not methamphetamine use, in treatment seeking individuals with methamphetamine dependence (Galloway et al., 2011). Rivastigmine, a cholinesterase inhibitor, was observed to reduce participant's endorsement of "Likely to Use Meth" when exposed to acute methamphetamine via intravenous infusion in a sample of non-treatment seeking methamphetamine dependent individuals (De La Garza et al., 2012). Buproprion, an antidepressant which inhibits the reuptake of dopamine and norepinepherine, has also been associated with reduced methamphetamine craving in response to video cues in a laboratory model of non-treatment seeking individuals with a methamphetamine use disorder (Newton et al., 2006). Nicotine has shown promise in rodent models of craving. Specifically, methamphetamine-seeking behavior was found to be attenuated by repeated nicotine administration during methamphetamine withdrawal. Further, this attenuating effect was antagonized by the nicotinic antagonist mecamylamine (Hiranita et al., 2004).

Naltrexone (12.5 and 50mg) was associated with a decrease in cocaine craving, but not positive subjective effects, during acute cocaine and d-amphetamine (versus placebo) administration in a sample comprised of predominant cocaine users (Comer et al., 2013). With respect to methamphetamine craving specifically, preclinical work suggests naltrexone inhibits reinstatement of drug-seeking behavior, a plausible marker of drug craving in the animal, induced by methamphetamine-associated cues in mice following 12 days of methamphetamine self-administration and extinction (Anggadiredja et al., 2004). These results were related to the changes in dopamine and dopamine metabolite levels (Lan et al., 2008), as well as to the binding of a D1 agonist and D2 antagonist (SKF38393 and sulpiride, respectively) to dopamine receptors in the striatum (Tien et al., 2007). Naltrexone was found to have no effect on methamphetamine-priming-induced reinstatement, possibly indicating a separate pathway for drug priming effects (Anggadiredja et al., 2004). Further, μ-opioid

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receptor knockout mice are unaffected by methamphetamine-induced behavioral sensitization (Shen et al., 2010), suggestive of naltrexone's mechanism of action in craving instatement. The blockage of methamphetamine-induced dopamine release in the mesolimbic dopamine system has been proposed as the neural mechanism underlying naltrexone's effect on cue-induced craving (Ashenhurst et al., 2012; Jayaram-Lindstrom et al., 2004); however, no study to date has been conducted in humans to test this hypothesis.

In summary, a number of pharmacotherapies are currently under study for the treatment of methamphetamine use disorders, many with promising preliminary results. Treatment development for methamphetamine use disorders, both behavioral and pharmacological, has been a challenging enterprise, yet consistent with the addiction field broadly (Litten et al., 2012) efforts to refocus the field towards medications with novel therapeutic targets hold considerable promise for this complex disorder.

6. Conclusions and Future Directions

Methamphetamine, a potent central nervous system stimulant, continues to pose a significant public health problem in the U.S. and worldwide. At present, the burden of care associated with methamphetamine use far exceeds what would be expected given the prevalence estimates, underscoring the pervasive impairments associated with methamphetamine use and addiction. Importantly, the culmination of recent prevalence, production, and supply reports warn of the potential for a “second wave” of increased methamphetamine use and associated problems, thus indicating the immediate need for advancements in basic and clinical methamphetamine research.

Through its actions on the brain's major dopaminergic, noradrenergic, serotonergic, and opioidergic pathways, repeated use of methamphetamine is associated with significant neurotoxic effects and neurocognitive deficits, with only a few of such effects known to remediate following sustained abstinence. Thus, early identification of problematic methamphetamine use and effective treatment implementation is critical to successful outcomes. Unfortunately, the available treatments for methamphetamine dependence are at best only modestly effective. There is modest evidence for the efficacy of psychosocial interventions, cognitive behavioral therapy (CBT) in particular; however, these treatments are time-intensive, expensive, and the outcomes are relatively poor at longer follow-up periods. Furthermore, there are no medications currently approved by the FDA to treat methamphetamine use disorders.

Following what appears to be a sequence of failures in medication development for methamphetamine dependence, the field has engendered renewed interest in the development of medications with novel molecular targets (e.g., enndocanabinoid and opioidergic systems, neuroinflammation; Brensilver et al., 2013; Snider et al., 2013; Vocci and Appel, 2007). Increasing evidence for the opioidergic system's role in the development (i.e., via reinforcement mechanisms) and maintenance (i.e., craving) of stimulant addiction has advanced pharmacologic agents targeting this pathway as plausible treatments for methamphetamine use disorders. Further, the few medications that have shown some promise for the treatment of methamphetamine use disorders, namely buproprion, modafinil,

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and naltrexone (as identified by this review), may exhibit greatest effectiveness through novel mechanisms such as enhancing the effectiveness of existent psychosocial interventions (e.g., via decreasing cognitive impairment) and by targeting intermediate phenotypes of addiction (e.g., relapse prevention/craving) (NIDA, 2005). Much more targeted, well-controlled research is indicated to fully understand the mechanisms and potential efficacy of these agents in the treatment of methamphetamine use disorders specifically, particularly given that these medications were commonly studied in small trials, distinct subpopulations, and/or predominately amphetamine using samples.

A number of gaps remain in the treatment literature for methamphetamine addiction. As described above, research is critically needed in pharmacologic treatment development (NIDA, 2005), particularly with novel targets and potentially novel delivery systems (e.g., vaccines; Kosten et al., 2014). By integrating basic neuroscience into treatment development research, one may elucidate how these novel interventions function to reduce methamphetamine use. This would allow in turn for the evaluation of neurotoxic and neurocognitive effects of prolonged methamphetamine use in the context of treatment outcomes and enable the identification of biomarkers with predictive validity. Further, given the poor retention rates, difficulties with treatment adherence, and overall poor outcomes associated with the interventions currently available, it is possible that the outpatient model employed for the treatment of many drugs of abuse is not suitable for methamphetamine addiction. If so, robust treatments studied within controlled inpatient/partial inpatient programs may prove more fruitful. As highlighted by this review and consistent with some conclusions reached by NIDA's Methamphetamine Addiction Treatment Think Tank (NIDA, 2005), research endeavors on the identification of biomarkers (to predict treatment response), relapse prevention (i.e., managing craving and stress), and remediation of associated cognitive impairment are advanced as crucial gaps in the knowledge base. Future research that can systematically address these gaps are thought to provide a roadmap for effective treatment development for methamphetamine addiction.

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Highlights

- Methamphetamine continues to pose a significant public health problem in the U.S.
- The review provides an update to the literature on methamphetamine use and addiction
- Current treatments for methamphetamine dependence are only modestly effective
- Future directions include development of medications with novel molecular targets

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Bupropion Attenuates Methamphetamine Self-Administration in Adult Male Rats

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Abstract

Bupropion is a promising candidate medication for methamphetamine use disorder. As such, we used a preclinical model of drug-taking to determine the effects of bupropion on the reinforcing effects of methamphetamine (0.025, 0.05 or 0.1 mg/kg/infusion). Specificity was determined by investigating the effects of bupropion on responding maintained by sucrose. In the self-administration study, rats were surgically prepared with indwelling jugular catheters and trained to self-administer methamphetamine under an FR5 schedule. A separate group of rats was trained to press a lever for sucrose. Once responding stabilized, rats were pretreated with bupropion (0, 10, 30 and 60 mg/kg IP) 5 min before chamber placement in a unique testing order. Following acute testing, rats were then repeatedly pretreated with 30 and 60 mg/kg bupropion. Acute treatments of bupropion dose dependently reduced drug intake for 0.025 to 0.1 mg/kg methamphetamine; sucrose deliveries were only reduced with the high bupropion dose. Repeated exposure to 60 mg/kg bupropion before the session resulted in a consistent decrease in methamphetamine intake (0.05 and 0.1 mg/kg) and sucrose deliveries. Considered together, this pattern of findings demonstrates that bupropion decreases responding for methamphetamine, but the effects are only somewhat specific.

Keywords

stimulant; substance use disorder; Wellbutrin; Zyban; reinforcement

1. Introduction

Methamphetamine is a highly potent, addictive drug that is widely abused in many countries around the world. In the United States, nearly 18 million people aged 12 and over (6% of the population) have tried methamphetamine in their lifetime and 700,000 of these individuals used some form of the drug within the last month (Substance Abuse and Mental Health Services Administration, 2007). Initially, methamphetamine produces a general state of well-being along with increased wakefulness, talkativeness, and physical activity and

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decreased appetite (NIDA, 2006). However, recreational use is often replaced with compulsive drug use, leading to addiction. Behavioral treatment programs have had some success in the treatment of methamphetamine addiction (Ling et al., 2006; Roll, 2007), yet many patients continue to relapse after repeatedly seeking treatment (NIDA, 2006). Thus, pharmacotherapies to compliment existing cognitive and behavioral treatments for methamphetamine addiction are being evaluated.

Numerous drugs from several different classes show promise as candidate medications for methamphetamine abuse (see Ling et al., 2006; Vocci and Appel, 2007 for reviews). One drug in particular, already approved by the U.S. Food and Drug Administration for use in humans is bupropion hydrochloride. Bupropion is an atypical antidepressant with stimulant properties used for the treatment of depression and smoking cessation (see Dwoskin et al., 2006 for a review). This drug has been used off-label to treat methamphetamine addicts, thus prompting the need for systematic investigations of its efficacy (Newton et al., 2006). The early clinical findings are promising. For example, bupropion treatment (twice daily, 150 mg, sustained release) was well tolerated in patients that received intravenous methamphetamine infusions (0, 15, or 30 mg) and by those abstaining from methamphetamine use (Elkashef et al., 2008; Newton et al., 2005). Additionally, bupropion reduced the subjective effects and cue-induced cravings of methamphetamine (Newton et al., 2006), and increased duration of abstinence in male participants classified as having “mild-to-moderate” methamphetamine dependence (Elkashef et al., 2008).

Preclinical behavioral and neurochemical studies support the theoretical bases and clinical findings for the use of bupropion to treat methamphetamine use disorder. Neurochemical studies demonstrated that bupropion treatment had neuroprotective effects against methamphetamine-induced neurotoxicity (Marek et al., 1990) and protected against the acute reduction of dopamine uptake in striatal synaptosomes (Kim et al., 2000). In locomotor activity studies with rodents, administration of intraperitoneal (IP) bupropion (12.5, 25, and 50 mg/kg) dose-dependently blocked methamphetamine-induced stereotypy in mice when methamphetamine followed bupropion (Muley et al., 1984). When methamphetamine preceded bupropion, methamphetamine-induced stereotypy was augmented (Muley et al., 1984). Additionally, a self-administration study with *d*-amphetamine (0.2 mg/kg/infusion) found that bupropion pretreatment decreased drug intake in rats (Rauhut et al., 2003). Most directly relevant to the present research is the finding from our laboratory that bupropion (60 mg/kg, IP) decreased the number of methamphetamine (0.025 mg/kg) infusions taken during acquisition and prevented rats from discriminating between the active and inactive levers (Reichel et al., 2008). Further, an acute administration of 30 mg/kg bupropion decreased the number of infusions in rats trained to self-administer 0.025 mg/kg/infusion methamphetamine. Taken together, these studies clearly indicate that bupropion and methamphetamine interact on a neurochemical and behavioral level.

There has been limited research concerning the impact of bupropion on methamphetamine self-administration given its consideration as a pharmacotherapy for methamphetamine abuse. Our previous research report demonstrated that bupropion can decrease drug intake (0.025 mg/kg); the goal of the present research was to extend this finding to various doses of self-administered methamphetamine to determine whether higher and presumably more rewarding doses would also be affected by bupropion pretreatment. In the first experiment, we evaluated bupropion’s impact during maintence of methamphetamine (0.025, 0.05, or 0.1 mg/kg/infusion) self-administration using acute and repeated bupropion pretreated protocols. In the second experiment, bupropion’s specificity for methamphetamine was assessed with rats whose responding was maintained by sucrose.

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2. General Methods

2.1. Subjects

Thirty-six male, Sprague-Dawley rats weighing 275–300 g at the time of delivery from Harlan (Indianapolis, IN, USA) were housed individually in clear polycarbonate tubs lined with wood shavings in a temperature and humidity controlled room. Water was continuously available in the home cage; access to food was restricted as described later. All sessions were conducted during the light portion of a 12 h light:dark cycle. Experimental protocols were approved by the University of Nebraska-Lincoln Institutional Animal Care and Use Committee and followed the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 1996).

2.2. Apparatus

Eight standard conditioning chambers (Med-Associates, Georgia, VT, USA) were used. Each chamber was housed in a PVC sound-attenuating cubicle fitted with a fan to provide airflow and mask noise and a house light to provide general illumination. Each chamber (30.5 × 24.1 × 21 cm; l × w × h) had side walls made of aluminum; the ceiling and front and back walls were clear polycarbonate. Located in the bottom center of one aluminum wall was an opening to a recessed dipper receptacle (5.2 × 5.2 × 3.8 cm; l × w × d). The dipper arm, when raised, allowed access to 0.1 ml of 26% sucrose solution (w/v). An infrared emitter/detector unit located 1.2 cm inside the receptacle and 3 cm above the floor recorded head entries. A second infrared emitter/detector unit was mounted on the center of the front and back polycarbonate wall, 4 cm above the rod floor, such that it bisected the chamber into two halves. The number of times this infrared beam was interrupted served as a measure of activity in the chamber. Retractable levers were located on either side of the dipper receptacle. Levers were set such that 147 nN of force was required for micro-switch closure and recording of a lever press. A white cue light (2.54 cm dia; 28 V, 100 mA) was centered 7 cm above each lever, 14.6 cm above the metal rod floor and 3.5 cm from the closest polycarbonate wall. Each chamber was equipped with a balanced metal arm and spring leash attached to a swivel. Tygon® tubing AAQ04103 (VWR, West Chester, PA, USA) extended through the leash and was connected to a 5-ml syringe mounted on an infusion pump (Med Associates, PMH-100VS) located outside of the sound-attenuating cubicle.

2.3. Drugs

D-methamphetamine hydrochloride was purchased from Sigma (St. Louis, MO, USA). Bupropion hydrochloride was purchased from Toronto Research Chemicals (Toronto, ON, Canada). Methamphetamine was dissolved in 0.9% sterile saline (w/v). Bupropion was dissolved in sterile water. Bupropion was administered IP at a volume of 1 ml/kg. Methamphetamine was administered intravenously (IV) at a volume of 35.74 µl per infusion.

2.4. Catheter Surgery and Recovery

Rats were anesthetized with 1 ml/kg ketamine hydrochloride (100 mg/ml, IP) followed by 0.6 ml/kg xylazine hydrochloride (20 mg/ml, IP) (Midwestern Veterinary Supply, Des Moines, IA, USA). One end of a silastic catheter (CamCaths© IVSA28, Ely, Cambridgeshire, United Kingdom) was implanted into the left external jugular vein. The other end of the catheter went subcutaneous around the shoulder and exited via a polycarbonate back-plate implanted under the skin just below the scapula. This backmount allowed access to the catheter through a metal cannula embedded with a plastic bolt. Buprenorphine hydrochloride (0.1 mg/kg; Sigma) was injected subcutaneously immediately following surgery. For the evening of and day following surgery buprenorphine (0.5 mg/kg,

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mixed at a concentration of 0.175 mg/40 ml) was available in the drinking water to manage post-surgical pain. For the evening after surgery and the following 2 days (AM and PM), the catheter was flushed with 0.1 ml of streptokinase (ca. 8000 Units/ml; Sigma) dissolved in sterile heparinized saline (30 Units/ml; Midwest Veterinary Supply). The catheter was flushed twice a day for the remainder of the experiment with 0.2 ml of the heparinized saline. Rats were allowed 5 days of recovery before the start of the experiment. Catheter patency was assessed with a 0.05 ml IV infusion of xylazine (20 mg/ml) at pre-established points in the study. This concentration produces clear motor ataxia within 5 sec if the catheter is patent. Only rats with patent catheters were included in the data analyses.

3. Procedures

3.1. Experiment 1: Bupropion Pretreatment on Methamphetamine Self-administration

3.1.1. Preliminary Training—All rats were allowed to acclimate to the colony room and then handled for 2 min each on 3 separate days before the start of training. Rats were fed 20 g of chow per day during the initial training period. Following handling, rats were dipper trained. Dipper training entailed a 50-min automated session in which the probability of receiving 4-sec access to sucrose in any 4-sec interval was 0.1333 (ca. 3 deliveries per min). For the two days following dipper training, rats were autoshaped to lever press. On a given session only one retractable lever (right or left) was inserted into the chamber for 15 sec using a variable time 60-sec schedule. If a lever press occurred before the 15 sec, the lever was retracted and the dipper was raised allowing 4-sec access to 0.1-ml sucrose. If no lever press occurred after 15 sec, the lever was retracted and 4-sec access to sucrose was still provided. The order of lever presentation was counterbalanced such that the left lever was extended during the first session for half the rats and the right lever for the remaining rats. For all rats, each session ended after 60 sucrose deliveries; session length varied somewhat between rats depending upon when consistent lever pressing developed in the session (ca. 80-min). After concluding the last autoshaping session, rats were allowed free access to rat chow until the end of the surgical recovery period.

3.1.2. Methamphetamine Self-Administration—Twenty-seven (9 per group) rats were assigned to one of three methamphetamine doses (0.025, 0.05, or 0.1 mg/kg/infusion) in a manner that counterbalanced all experimental variables (e.g., which lever served as the active lever, chamber, etc) as much as the sample size allowed. Sessions were 60 min and the house light remained on throughout the session. Pressing the active lever resulted in a 1-sec illumination of the cue light above the active lever and a simultaneous 1-sec infusion of the assigned methamphetamine dose [i.e., a fixed ratio 1 (FR1) schedule of reinforcement]. Following an active lever press, both levers were retracted for 1 min. Pressing the inactive lever had no programmed consequence. The schedule of reinforcement was increased automatically from an FR1 (8 days) to an FR3 (5 days) then to an FR5 (5 days). However, rats were advanced to the next FR requirement early if they met the following criteria: number of infusions within 20% of each other for 2 consecutive days and 2:1 ratio of active to inactive lever presses.

3.1.3. Bupropion Acute Challenges—When responding stabilized on an FR5, rats entered the acute testing phase. Each rat was tested with a unique order of vehicle, 10, 30, and 60 mg/kg bupropion. Each solution was administered IP 5 min before placement in the chamber for a regular self-administration session and each test was separated by at least 2 maintenance days of methamphetamine self-administration without drug pretreatment. To meet test criteria, rats were required to have 2 consecutive days in which the number of infusions was within 20% of each other. After all doses of bupropion were tested, catheter

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patency was checked. Rats with patent catheters were then advanced to the next experimental phase.

3.1.4. Bupropion Repeated Testing—The repeated testing portion of the experiment consisted of 4 consecutive phases defined by the pre-injection of vehicle or bupropion. The following describes the specific phases. 1) The first 3 days were methamphetamine self-administration maintenance sessions that occurred following an injection of vehicle 5 min before chamber placement. 2) For the following 3 days rats were pretreated with 30 mg/kg bupropion 5 min before chamber placement for a regular self-administration session. 3) For the following 5 days rats were pretreated with 60 mg/kg bupropion 5 min before chamber placement for a regular self-administration session. 4) The last phase consisted of 5 maintenance days, in which vehicle was administered before the session. Following completion of this repeated testing schedule, a final patency check was conducted.

3.2. Experiment 2: Bupropion Pretreatment on Sucrose-Maintained Responding

3.2.1. Preliminary Training—A separate set of naïve rats (n=8) were used in this experiment. These rats also had 3 consecutive days of preliminary training consisting of one dipper training session and two autoshaping sessions as described previously. Following the last autoshaping session, rats were given free access to food and kept in their home cages for 5 days to simulate the surgical recovery period for the self-administration experiment. This experiment did not require surgery but all other experimental parameters (e.g., handling, start of acquisition, feeding, etc.) were matched with Experiment 1.

3.2.2. Sucrose-Maintained Responding—The procedures for the sucrose experiment were identical to those just described for the self-administration study except that instead of an infusion of methamphetamine, active lever presses resulted in 4-sec access to 0.1-ml sucrose. The exact protocol of Experiment 1 was followed for all phases of Experiment 2.

3.3 Dependent Measures and Data Analysis

The number of methamphetamine infusions (Experiment 1) or sucrose deliveries (Experiment 2) served as the main dependent measures. To assess non-specific effects of bupropion, the number of inactive lever presses and general chamber activity were also analyzed. Only data from rats that had patent catheters at the end of each experimental phase were used in the statistical analyses; the number of rats in each analysis is provided in the Results section. Some rats that were assigned to the 0.025 mg/kg/infusion group did not maintain responding on an FR5 schedule; schedules were adjusted for individual subjects until responding stabilized. In total, 3 rats stabilized on an FR1, 1 rat on an FR3, and 3 rats on an FR5.

Data from each experiment were analyzed with analyses of variance (ANOVAs). Depending upon the specific experimental phase, the between-subjects factor was methamphetamine dose and the within-subject factors were bupropion dose or session. For the repeated testing phase, an average of the 3 consecutive days (before repeated testing began) of methamphetamine self-administration or sucrose-maintained responding was used for a baseline. An average of the 5 days after repeated testing was calculated for comparison purposes to determine if responding returned to baseline after bupropion exposure ceased. In the first experiment, the number of methamphetamine infusions, inactive lever presses, and activity counts were analyzed with separate two-way (Methamphetamine × Bupropion) mixed ANOVAs for the acute bupropion tests. For the repeated bupropion testing, a two-way (Methamphetamine × Session) mixed ANOVA was conducted. A significant interaction was followed by separate one-way (Session) ANOVAs for each methamphetamine dose. In the second experiment, the number of sucrose deliveries, inactive lever presses, and activity

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counts were analyzed with separate one-way (Bupropion) ANOVAs for the acute bupropion tests. Repeated bupropion testing was analyzed by a one-way (Session) ANOVA. Only the significant effects are reported. In all cases, significant interactions were interpreted with Fisher's least significant difference (LSD) tests for post-hoc comparisons. Statistical significance was set at $p<0.05$ (two-tailed) for all tests.

4. Results

4.1. Experiment 1: Methamphetamine Self-Administration

4.1.1 Bupropion Acute Testing—Bupropion reduced methamphetamine infusions regardless of the self-administration dose [Figure 1A, main effect of Bupropion, $F(3,36)=28.73$, $p<.001$]. Specifically, 30 and 60 mg/kg bupropion decreased the number of methamphetamine infusions compared to vehicle and 10 mg/kg bupropion (LSD_{mmd} = 5.19). Figure 1B shows the impact of bupropion on inactive lever presses. Although the overall analysis suggested a reduction in responding [main effect of Bupropion, $F(3,36)=4.10$, $p<0.01$], differences did not emerge with the post-hoc analysis (LSD_{mmd} = 6.79). Bupropion had no impact on general chamber activity during methamphetamine self-administration (Figure 1C). A total of 21 rats (0.025 n=7; 0.05 n=6; 0.1 n=8) were used in this analysis.

4.1.2. Bupropion Repeated Testing—Repeated bupropion exposure produced a reduction in methamphetamine infusions depending upon the methamphetamine training dose and the bupropion test dose [Figure 2A, Methamphetamine × Session interaction, $F(16,136)=2.75$, $p<0.001$]. In particular, when 0.025 mg/kg methamphetamine (n=6) was the training dose, 30 mg/kg bupropion decreased infusions the first day of administration and 60 mg/kg bupropion had a similar effect the first and second day it was given [Figure 2B, $F(8,40)=3.99$, $p<0.001$; LSD_{mmd} = 7.76]. In contrast, for the 0.05 mg/kg methamphetamine (n=6) group, only 60 mg/kg bupropion decreased infusions on days 1, 3, 4, and 5 relative to baseline [Figure 2C, $F(8,40)=4.06$, $p<0.001$; LSD_{mmd} = 5.51]. Finally, 30 and 60 mg/kg bupropion decreased infusions throughout the repeated testing phase when 0.1 mg/kg methamphetamine (n=8) was the training dose [Figure 2D, $F(8,56)=4.00$, $p<0.001$]. Specifically, 30 mg/kg bupropion reduced infusions on days 1 and 2, and 60 mg/kg bupropion reduced infusions on all 5 days (LSD_{mmd} = 2.61). For all methamphetamine doses, discontinuing bupropion pretreatment resulted in a return to baseline methamphetamine intake (individual paired t-tests between pre and post baseline responding, $ts<1$). Bupropion did not impact inactive lever responding during repeated treatment for any of the methamphetamine doses (see Table 1). There was a tendency for activity in all three methamphetamine groups to decline over the sessions [see Table 2, main effect of Session, $F(8,136)=8.50$, $p<0.001$]. Specifically, 60 mg/kg bupropion pretreatment on day 5 decreased activity relative to baseline [mean ± SEM: Baseline = 690.87 ± 56.36; Bupropion day 5 = 503.03 ± 61.43; LSD_{mmd} = 181.0].

4.2 Experiment 2: Sucrose-Maintained Responding

4.2.1 Bupropion Acute Testing—The high dose of bupropion, 60 mg/kg, produced a decrease in sucrose deliveries relative to vehicle, 10, and 30 bupropion [Figure 3A, main effect of Bupropion, $F(3,21)=11.58$, $p<0.001$; LSD_{mmd} = 13.01]. Bupropion did not, however, impact inactive lever presses (Figure 3B). One rat pressed the inactive lever over 1100 times; over 2 standard deviations from the mean. As such, this value was excluded from the inactive lever analysis. Bupropion increased activity during the session [Figure 3C, Bupropion effect, $F(3,21)=5.52$, $p<0.006$]. Specifically, 30 and 60 mg/kg bupropion resulted in higher activity counts relative to vehicle and 10 bupropion (LSD_{mmd} = 193.29).

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2.2.2 Bupropion Repeated Testing—Bupropion reduced the number of sucrose deliveries [Figure 3D, Session effect, $F(8,56)=2.28$, $p<0.05$]. Specifically, 30 mg/kg bupropion reduced deliveries on the first day of administration whereas, 60 mg/kg bupropion decreased deliveries on days 1 through 5 (LSD_{mmd} =14.55). Discontinuing bupropion pretreatment resulted in a return to baseline sucrose deliveries (paired t-test between pre and post baseline responding, $t<1$). Bupropion did not impact inactive lever responding during repeated treatment (see Table 1), nor did it not significantly affect chamber activity during repeated testing (see Table 2).

Discussion

In the present study we investigated the effects of acute (vehicle, 10, 30, and 60 mg/kg) and repeated (30 and 60 mg/kg) bupropion treatment on 3 different doses of methamphetamine self-administration and responding for sucrose. We found that acute administration of 30 and 60 mg/kg bupropion decreased intake of 0.025, 0.05, and 0.1 mg/kg/infusion of methamphetamine. More so, the highest dose of bupropion also decreased sucrose deliveries. Repeated administrations of 30 and 60 mg/kg bupropion reduced methamphetamine infusions differentially across session depending upon the training dose. Lever pressing for sucrose was also decreased across test sessions with 30 and 60 mg/kg bupropion pretreatment. Importantly, in all instances these reductions in response to methamphetamine and sucrose as reinforcers were independent of changes in inactive lever presses and mostly unaffected by activity during the session.

Earlier reports show that bupropion reduced intake of nicotine, amphetamine, and methamphetamine (Buijnzeel and Markou, 2003; Rauhut et al., 2003; Reichel et al., 2008). We extend these findings to include multiple doses of methamphetamine during acute and repeated exposure. That bupropion decreased intake of various stimulant drugs indicates some level of non-specificity in its action on abused drugs. Bupropion has been shown to be an antagonist at nicotinic acetylcholine receptors (Slemmer et al., 2000), and blockade of these receptors prevents the induction of behavioral sensitization to amphetamine (Schoffelmeer et al., 2002) and decreases nicotine and methamphetamine intake (Hiranita et al., 2006; Watkins et al., 1999). These studies used the potent and nonspecific nicotinic antagonist mecamylamine. In contrast, bupropion is a relatively weak antagonist particularly at α7-containing nicotinic acetylcholine receptors (Slemmer et al., 2000). For this reason, we believe that nicotinic acetylcholine receptor antagonism seems an unlikely candidate to explain bupropion mediated decrease in methamphetamine self-administration in the present study. Alternatively, methamphetamine and bupropion increase dopaminergic neurotransmission in brain reward pathways (Kuczenski et al., 1995; Melega et al., 1995; Nomikos et al., 1989; 1992). This similar mechanism results in substitution of the drug effects (Munzar and Goldberg, 2000; Reichel et al., 2007) that may reduce drug intake (Munzar et al., 1999). This dopaminergic mechanism is also appealing because it also provides a potential common process to explain our sucrose findings. That is, blockade of nicotinic acetylcholine receptors does not typically decrease sucrose-maintained responding (Nadal, et al., 1998; Pratt and Kelly, 2004), but blockade of dopamine receptors does (Beninger et al., 1987, Ikemoto and Panksepp, 1996; Johnston et al., 2001).

Repeated bupropion testing also decreased methamphetamine and sucrose-maintained responding. Bupropion (30 mg/kg) only transiently reduced methamphetamine intake and sucrose deliveries suggesting decreased effectiveness across administration. This decrease also developed with 60 mg/kg bupropion for the 0.025 mg/kg methamphetamine group. In contrast, 60 mg/kg bupropion also decreased methamphetamine (0.05 and 0.1 mg/kg) infusions and sucrose deliveries earned throughout the repeated testing sessions. Notably, reductions in sucrose deliveries resulting from repeated bupropion pretreatment have been

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reported previously (Rauhut et al., 2005). Importantly, any bupropion-induced changes in sucrose or food maintained responding must consider the anorexic effects of the drug. Bupropion is prescribed for the treatment of obesity in humans (Gadde et al., 2001) and reduces food intake in laboratory animals (Zarrindast and Hosseini-Nia, 1988). Thus, repeatedly administering 60 mg/kg bupropion may have had an anorexic effect for rats in the sucrose experiment. The question remains as to whether the bupropion-induced decrease in sucrose deliveries is independent of bupropion's effects on the reward system.

Responding on the inactive lever was not altered whether methamphetamine or sucrose served as the reinforcer. Further, inactive lever responding was relatively stable in both experiments even when bupropion pretreatment occurred across consecutive days. This finding contrasts with Rauhut and colleagues (2003) in which bupropion (15–78 mg/kg) reduced inactive lever presses, but is in accordance with Bruijnzeel and Markou (2003) where bupropion did not change inactive lever presses. Nevertheless, the current findings question any account of the bupropion-induced decrease in responding maintained by methamphetamine or sucrose that relies on a generalized alteration of lever pressing.

Acute administration of bupropion increases locomotor activity in rodents (Cooper et al., 1980; Nomikos et al., 1992; Wilkinson & Bevins, 2007). More so, locomotor stimulation is maintained and sometimes enhanced with repeated administration (Cooper et al., 1980; Nielsen et al., 1986). The ability of a locomotor stimulating drug, in our case bupropion, to reduce responding for a reinforcer raises concerns about the competitive nature of the concurrent behaviors (Robbins and Sahakian, 1979). That is, with more time spent engaged in locomotion, there is less time available to lever press and complete the FR requirements. This competing locomotor account can explain the reduction of sucrose deliveries observed with 60 mg/kg bupropion because this dose simultaneously increased chamber activity. However, a competing locomotor account cannot wholly explain the reductions in sucrose deliveries for two specific reasons. First, during the acute testing with 30 mg/kg bupropion the number of sucrose deliveries were not affected but activity increased. Second, repeated bupropion treatment decreased sucrose responding but did not significantly impact activity.

The attenuation of methamphetamine self-administration during the acute challenges was not likely due to bupropion-induced increases in chamber activity because activity did not differ with bupropion pretreatment dose. As such, the combined effects of bupropion and self-administered methamphetamine produced similar locomotor activating effects. There was, however, an interesting pattern of the activity with repeated testing. Daily pretreatment with 60 mg/kg bupropion in combination with methamphetamine produced a decline in chamber activity. One possible reason for this decrease in general chamber activity is that the repeated exposure to bupropion preferentially induced stereotyped behaviors in a manner consistent with other stimulant drugs (Bhattacharyya and Pradhan, 1979; Kuczenski and Segal, 1989; Nomikos et al., 1989). Although stereotypy could explain the decrease in active lever responding, such behaviors were not measured in the present experiment. Thus, the exact mechanisms responsible for decreased activity and methamphetamine self-administration in this 60 mg/kg condition will require further investigation.

Any comparisons between the self-administration and sucrose experiment must take into account that sucrose engendered a higher rate of responding than methamphetamine (see Dews, 1958). Thus, the similar impact of 60 mg/kg bupropion on responding maintained by methamphetamine and sucrose may be partially influenced by differences in response rate. There is no way to avoid this difference with an FR5 schedule of reinforcement except by varying some other behavioral parameter (e.g., limiting the number of reinforcers available with a shorter session or longer timeout) along with the reinforcer. Some studies impose longer timeouts (cf. Neugebauer et al., 2007; Paterson et al., 2003), increase the response

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requirement, and/or manipulate the food deprivation schedule (Stairs and Dworkin, 2008) in the sucrose experiments meant to parallel drug self-administration studies. Unfortunately, making such a change in reinforcement schedule forces other factors to vary such as temporal pattern of responding and access to the reinforcer. The importance of these changes and how they interact with drug effects is unclear. With these considerations in mind, we examined the initial 15 min of the session as a way of assessing treatment as a function of a similar number of reinforcer deliveries in the test session. That analysis found the same bupropion-induced decline in reinforcers earned whether rate was adjusted for a similar number of reinforcer deliveries in the test session or left unadjusted. Additionally, any comparisons between the self-administration and sucrose experiment must take into consideration differences in the surgery procedures such as brief exposure to anesthesia and pain medication (i.e., sucrose rats did not undergo surgery) or the repeated stimulant exposure in the methamphetamine-taking rats.

The use of bupropion to treat methamphetamine addiction fits a treatment approach termed “agonist substitution” therapy (see Gorelick, 1998; Grabowski et al., 2004; Rothman et al., 2002). The most notable successes of this approach have been with methadone maintenance programs for heroin abusers or nicotine replacement therapies for tobacco users (see Grabowski et al., 2004; Lile 2006 for reviews). The potential value of these treatments prompts the exploration of substitution drugs for the treatment of methamphetamine use disorder. Typically, agonist medications share pharmacological mechanisms of action with the abused drug (Grabowski et al., 2004). As previously mentioned, bupropion and methamphetamine share interoceptive stimulus properties (Munzar and Goldberg, 2000; Reichel et al., 2007; Rush, et al., 1998) and they increase synaptic dopamine concentrations (Kuczenski et al., 1995; Melega et al., 1995; Nomikos et al., 1989; 1992). Bupropion does so by blocking reuptake of dopamine; interestingly drugs with this mechanism [e.g., GBR 12909 and 2-beta-propanoyl-3beta-(4_tolyl)-tropane] produced sustained and selective reductions in cocaine intake (Grabowski et al., 2004). Combined, the shared stimulus properties of methamphetamine and bupropion with the ability of dopamine reuptake inhibitors to reduce self-administered cocaine provide theoretical support that bupropion might be a viable choice as a substitution drug for methamphetamine. In fact, addicts often report using methamphetamine to “make them feel normal” (Bungay et al., 2006). Albeit speculative, bupropion may provide some aspects of this “normalization” to methamphetamine addicts.

To date our laboratory has demonstrated that bupropion impacts methamphetamine self-administration during acquisition (Reichel et al., 2008) and now during a maintenance phase (current study). While this information combined with results of early clinical reports indicates that bupropion may be useful as a treatment for methamphetamine use disorder, several questions remain about bupropion’s impact during withdrawal, abstinence, and relapse in a preclinical setting. Research investigating these aspects of addiction will help provide a clearer picture on the effects of bupropion on methamphetamine self-administration in laboratory animals and methamphetamine abuse in humans.

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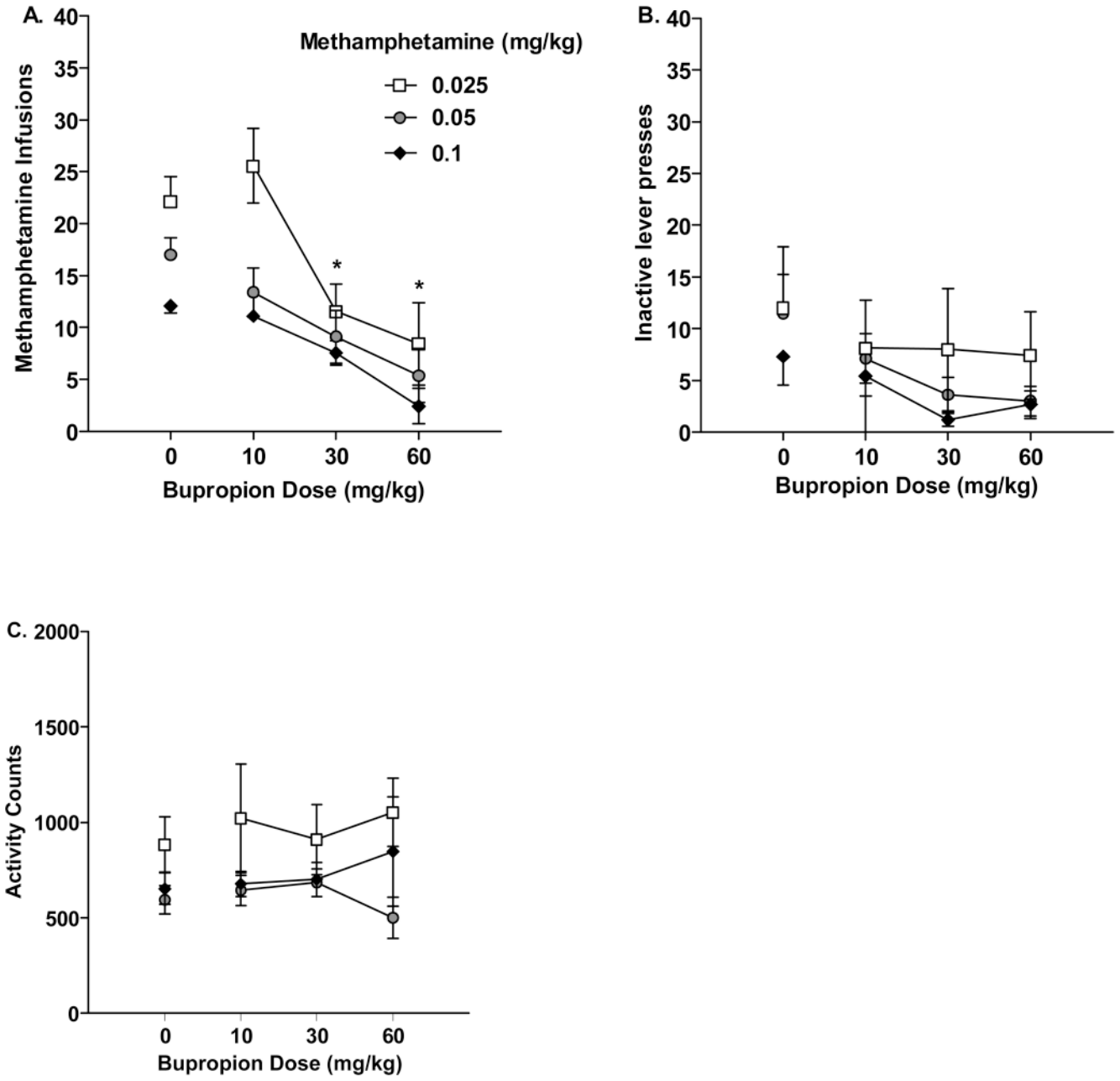

Figure 1.

A) Mean (±SEM) number of infusions for rats trained to self-administer 0.025, 0.05 and 0.1 mg/kg/infusion methamphetamine (ns= 7, 8, and 9, respectively) during acute testing with vehicle, 10, 30, and 60 mg/kg bupropion. Bupropion (30 and 60 mg/kg) decreased methamphetamine infusions. B) Mean (±SEM) responses on the inactive lever during acute testing. C) This graph illustrates the mean (±SEM) activity during the self-administration sessions. *Significant difference from vehicle and 10.

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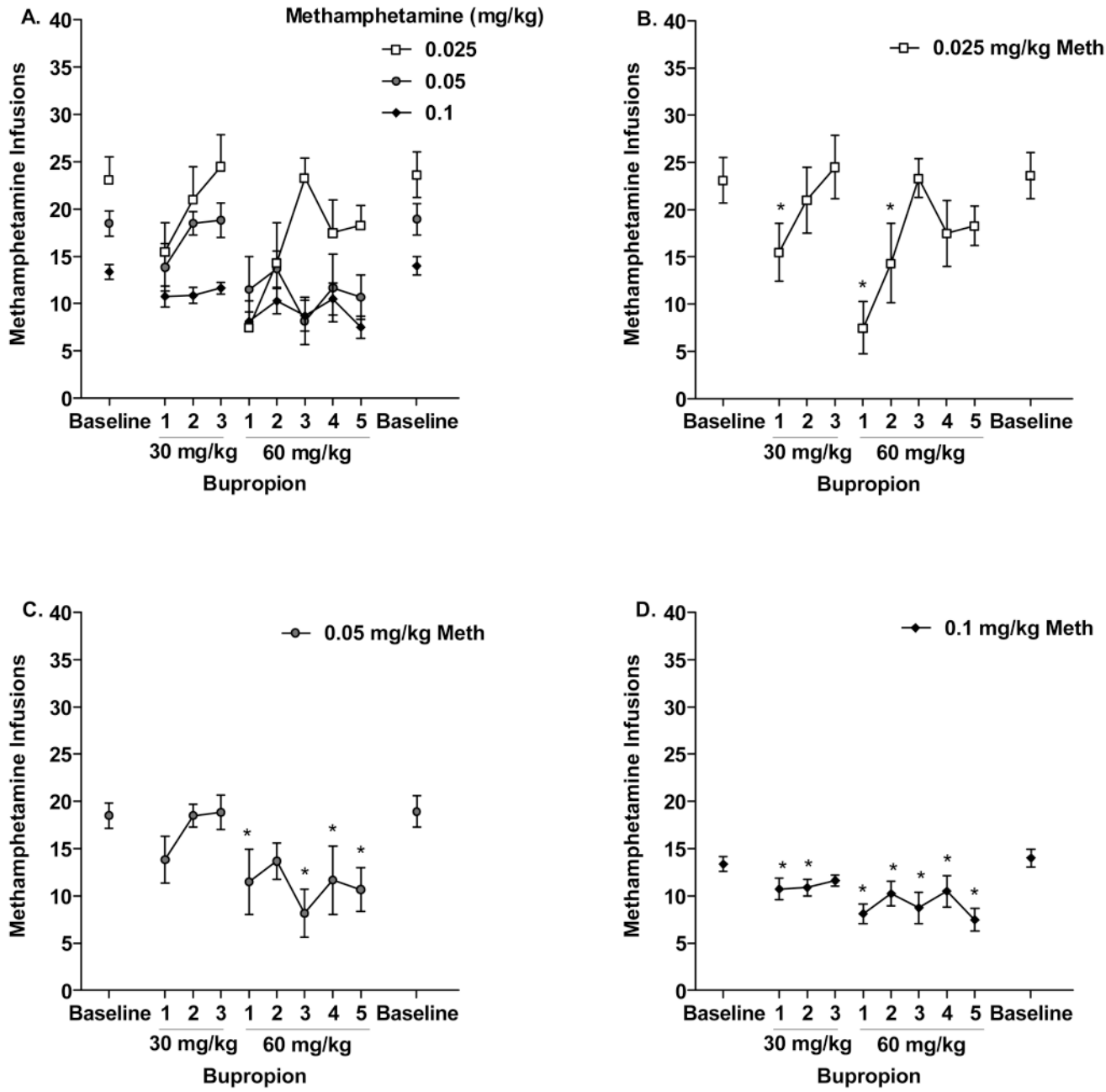

Figure 2.

A) Mean (±SEM) number of infusions for rats trained to self-administer 0.025, 0.05 and 0.1 mg/kg/infusion methamphetamine (ns= 6, 6, and 8, respectively) during repeated testing with 30, and 60 mg/kg bupropion. B) Repeated testing for rats in the 0.025 methamphetamine group, C) the 0.05 methamphetamine group, and D) the 0.1 methamphetamine group. *Significant difference from baseline.

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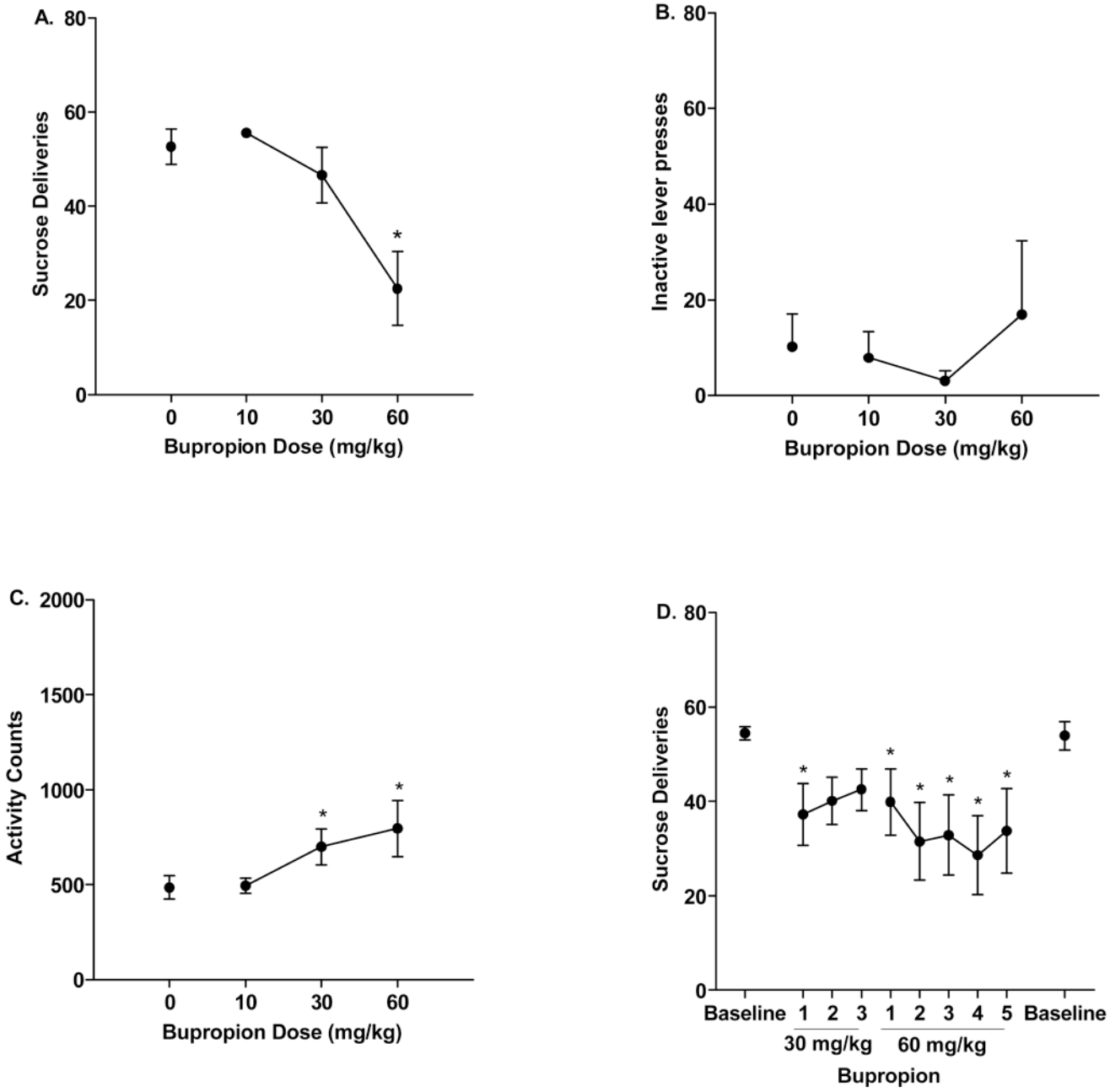

Figure 3.

Data from rats trained to lever press for sucrose reinforcement (n=8) during testing with bupropion. A) Mean (±SEM) number of sucrose deliveries during acute testing with vehicle, 10, 30, and 60 mg/kg. Reinforcers earned were decreased with 60 mg/kg bupropion. B) Mean (±SEM) responses on the inactive lever during acute testing. C) Mean (±SEM) activity during the self-administration sessions; bupropion (30 and 60 mg/kg) increased activity relative to vehicle. D) Mean (±SEM) number of sucrose deliveries during the repeated testing phase. *Significant difference from vehicle or baseline.

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Table 1

Inactive lever presses for rats trained with methamphetamine or sucrose during repeated testing with bupropion.

	Methamphetamine (or Sucrose) Group Mean ± SEM inactive lever presses			
Bupropion Dose (mg/kg)	**0.025**	**0.05**	**0.1**	**Sucrose**
Baseline	6.56 ± 1.59	11.17 ± 2.78	3.38 ± 1.17	9.21 ± 3.94
30 day 1	3.33 ± 2.03	4.67 ± 2.28	1.75 ± 1.146	60.62 ± 58.91
30 day 2	2.83 ± 1.30	4.00 ± 1.39	1.62 ± 1.34	15.75 ± 8.55
30 day 3	2.50 ± 1.28	2.83 ± 2.09	4.12 ± 1.59	4.00 ± 1.24
60 day 1	0.17 ± 0.17	3.50 ± 2.50	0.62 ± 0.42	4.12 ± 1.88
60 day 2	2.50 ± 1.57	18.00 ± 13.36	1.37 ± 0.62	3.12 ± 2.32
60 day 3	2.33 ± 1.23	16.17 ± 14.98	0.87 ± 0.64	3.13 ± 2.72
60 day 4	0.83 ± 0.40	4.83 ± 3.76	1.37 ± 0.65	3.63 ± 2.29
60 day 5	3.16 ± 1.68	9.83 ± 8.51	2.00 ± 1.08	4.87 ± 2.07
Baseline	5.67 ± 1.78	13.67 ± 4.86	4.10 ± 1.23	5.43 ± 2.48

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Table 2

Activity counts for rats trained with methamphetamine or sucrose during repeated testing with bupropion.

Bupropion Dose (mg/kg)	Methamphetamine (or Sucrose) Group Mean ± SEM chamber activity			
	0.025	0.05	0.1	Sucrose
Baseline	760.06 ± 145.39	667.50 ± 64.33	645.04 ± 73.45	433.00 ± 37.08
30 day 1	964.16 ± 195.86	835.66 ± 98.45	725.50 ± 48.54	604.75 ± 68.92
30 day 2	981.16 ± 150.61	705.00 ± 80.35	716.75 ± 83.17	614.87 ± 47.69
30 day 3	913.00 ± 160.74	629.83 ± 45.72	633.25 ± 81.72	556.37 ± 36.37
60 day 1	759.50 ± 213.23	505.66 ± 71.63	509.37 ± 86.48	483.50 ± 27.33
60 day 2	713.00 ± 118.21	553.83 ± 56.90	619.87 ± 99.67	513.25 ± 69.06
60 day 3	753.16 ± 124.75	499.66 ± 59.75	533.75 ± 83.77	489.25 ± 60.94
60 day 4	789.16 ± 157.86	486.66 ± 64.22	514.00 ± 56.93	533.00 ± 76.66
60 day 5	643.83 ± 154.18	400.00 ± 103.71	465.25 ± 63.19	432.12 ± 34.65
Baseline	643.10 ± 83.02	554.83 ± 36.59	622.93 ± 45.22	381.65 ± 34.48

Current Research on Methamphetamine: Epidemiology, Medical and Psychiatric Effects, Treatment, and Harm Reduction Efforts

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Review Article

Abstract

Background: Methamphetamine (MA) which is known as "shisheh" in Iran is a drug that widely is used in many parts of the world and it is near to a decade that is available for the most drug users and has a considerable prevalence of use. Due to high abuse prevalence and very new challenging phenomenon, it is very important that researchers and treatment providers become more familiar with different aspects of MA.

Discussion: It has multiple neurobiological impacts on the nervous system, some of which are transitory and some longer lasting. MA activates the reward system of the brain and produces effects that are highly reinforcing, which can lead to abuse and dependence. Routes of administration that produce rapid onset of the drug's effects (i.e., smoking and injection) are likely to lead to more rapid addiction and more medical and psychiatric effects. No effective pharmacotherapies have been developed for the treatment of MA dependence; although, this is an area of very active research. Several behavioral treatments have been shown to reduce MA use, but better treatments are needed.

Conclusion: Harm reduction strategies for non-treatment seeking MA users are needed to reduce the risk of human immunodeficiency virus and other medical risks. The research agenda for MA is substantial, with development of effective pharmacotherapies as one of the most important priorities. Appropriate and effective response for prevention, treatment and harm reduction services due to increasing problems regarding MA in Iran and some other countries in the region.

Keywords: Methamphetamine, Epidemiology, Side-effects, Treatment, Harm reduction, Iran

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Introduction

Worldwide, as many as 52 million individuals aged 15-64 are estimated to have used amphetamine-type stimulants for non-medical purposes at least once in the past year. Methamphetamine (MA) is the second most widely abused illicit drug in the world (following cannabis); its users nearly outnumber heroin and cocaine users combined. About two-thirds of the world's MA/amphetamine users reside in East and Southeast Asia, followed by approximately one-fifth in the Americas (specifically the United States and Northern Mexico).

Iran has a special situation in Asia and Middle East, with regard to amphetamine type stimulants (ATS) availability and use. Prior to 2004, there were no reported seizures of ATS in Iran. The first reported of ATS seizure was in 2005,[1] followed by an increasing number of seizures, year by year.[2-7] The amount of MA seized qualified Iran for ranking 5th in ATS seizures in 2010 and 2011.[6,7] There was a 400% increase in the amount of ATS seized in Iran between 2010 and 2011, this 1 year rate of increase compares to increases of 238% in Mexico 166% in Thailand, 153% in USA and 140% in China, put Iran in 1st ranking for an increase in seizure.

Discussion

Pharmacology of MA

MA increases activation of the dopamine, norepinephrine, and serotonin systems. MA use causes the release of dopamine into the synaptic cleft, increasing dopamine concentration. Furthermore, MA inhibits transport of dopamine into the storage vesicles, thus increasing the synaptic dopamine concentration. This abnormally high concentration of dopamine contributes to the severe neurotoxicity of MA. Heavy daily MA use and high dosages over a long duration result in neurobiological deficits that do not resolve until many months following cessation of use.[8–10]

Besides the acute dopaminergic stimulation, MA produces norepinephrine effects such as mild elevation of pulse and blood pressure and cutaneous vasoconstriction, but it is important to know that some chronic users shows a unpredictable hypotension during general anesthesia in operation rooms, which one of the possible cause is down-regulation of endogenous catecholamine receptors.[11]

Higher doses increase central nervous system stimulation, manifested as increased alertness and compulsive or repetitive behavior. MA users have increased sympathomimetic effects such as dizziness, tremor, hyperreflexia, pyrexia, mydriasis, diaphoresis, tachypnea, tachycardia, and hypertension.[12] The drug has a prolonged half-life (10-12 h) and long duration of action. Elevated levels of dopamine in the central nervous system are associated with the reinforcing and highly addictive properties of MA.

Route of administration

MA can be used orally or intranasal, or it can be smoked or injected intravenously. Injection and smoked administration of MA carry higher risk for acute toxicity as well as greater potential for the development of addiction. In general, the rapid onset of euphoria provided by these routes of administration provides a powerful stimulus for re-administration of the drug to maintain the euphoria. When injected intravenously, MA reaches cerebral circulation in 10-15 s. When smoked, it reaches the brain in 6-8 s; smoking can achieve blood levels comparable to those reached through intravenous injection.[13,14] These routes also have the most potential for toxicity due to rapid dose escalation. Intranasal insufflation (snorting) of MA produces euphoria in 3-5 min.[14] Absorption of orally administered MA occurs more slowly from the intestines, with peak plasma levels being reached 180 min after dosing.[15] Clinical reports recount dependence-level users taking 50 to 1000 mg of MA daily.

MA injection in Iran is reporting recently in different cities with high rate of injection and shared injection both in closed and open setting, which is an alarming sign for human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) prevention programs in Iran.[16–18]

Symptoms of MA use, misuse, and dependence

MA use increases blood pressure, body temperature, heart rate, and breathing rate. Continued use is common because of rewarding effects such as euphoria, reduced fatigue, reduced hunger, increased energy, increased sex drive, and increased self-confidence. Negative acute effects include abdominal cramps, shaking, high

body temperature, bruxism (teeth grinding), stroke, and cardiac arrhythmia, as well as increased anxiety, insomnia, aggressive tendencies, paranoia, and hallucinations.

The acute subjective effects of MA use depend on the amount used and route of administration. The effects of injection and smoking are rapid and intense, often described as a "rush," followed by euphoria and a sense of increased energy, wakefulness, alertness, and increased libido. Heart rate, blood pressure, and breathing rate increase and many users will grind their teeth and pick at their skin. Effects of MA can last up to 12 h. Due to the development of tolerance, chronic MA users repeat dosing every few hours in "binging" episodes, which can result in paranoia, hallucinations, delusions, mood disturbance, and formication (tactile hallucination of bugs crawling on the skin).

After prolonged or heavy use of MA, a withdrawal syndrome may emerge characterized by dysphoric mood, anhedonia, fatigue, increased appetite, sleep disturbance, and slowing, or acceleration of psychomotor activity.[19] The severity of withdrawal is related to the duration and intensity of recent MA use.[20] MA-dependent individuals have reported remission of the most severe withdrawal symptoms within several days to 3 weeks; although, there have been numerous clinical observations of more subtle symptoms (i.e., anhedonia) lasting for several months.[21,22] Apathy has been reported more frequently than depressed mood, suggesting that anhedonia may be more problematic than major depressive disorder following cessation of MA use.[23]

Psychiatric considerations

MA-associated psychiatric impairment may occur in several domains: cognitive, intellectual, or affective. The drug's contribution to impairment may be acute, delayed, or cumulative/residual. Psychiatric impairment appears to correlate with duration of use as well as total and peak amounts of MA absorbed. Neurocognitive deficits associated with chronic MA use include impairments in episodic memory, executive functions, and psychomotor tasks related to frontostriatal and limbic circuits. MA use may also be associated with deficits in attention, memory, and language.[24] Neurocognitive impairment may persist for 9 months or longer following cessation of MA use, but recovery in DAT activity and improvement in cognitive functioning is possible with sustained abstinence.[25–27]

Psychiatric symptoms have been well-documented in MA users.[27] Anxiety, depression, insomnia, and psychosis are among the most commonly reported symptoms associated with MA dependence, and individuals presenting to the emergency department in the context of MA intoxication may be agitated, violent, or suicidal.[28,29] Though minor agitation may be treated by placing the individual in a quiet, less stimulating environment, benzodiazepines, or neuroleptics may be required for more severe MA-related agitation or psychosis.[29]

Psychiatric symptoms may vary as a result of individual differences in sensitivity to MA, amount and/or frequency of use, and route of administration.[30] Individuals who use intravenously and who have a family history of psychotic symptoms are at heightened risk for the development of MA-related psychosis, which may mimic schizophrenia. Clinical symptoms of MA-induced psychosis include paranoia, delusions, and hallucinations.[31,32] Psychosis occurs at least intermittently in a significant proportion of MA users, with wide variation in the severity and clinical course of symptoms.[31]

Although the majority of MA-related psychiatric symptoms typically remit within a week of abstinence,[23] a subset of MA users experience prolonged psychiatric symptomatology, even in the absence of a prior reported history of mental illness.[33,34] Although MA is one of the most famous drugs in a drug-induced psychosis, but recent studies finding suggest that designer drugs may have severe side-effects in this domain than MA.[35]

Medical considerations

Chronic use of MA results in a variety of medical consequences, including cardiovascular disease, pulmonary problems, neurological problems, and dental disease. Long-term MA use is associated with elevated rates of infectious diseases, including HIV, hepatitis B and C, and endocarditis.[29] Factors mediating the relationship between MA use and infectious diseases include increased risky sexual behaviors occurring in the context of MA intoxication, as well as injection

drug use and associated risk behaviors (e.g., needle sharing).[36]

Clinical considerations

The groups disproportionately impacted by MA have been women and men who have sex with men (MSM). Unlike with cocaine and heroin, where a very high proportion of users are male, women use MA at rates almost equal to men. Surveys among women suggest that they are more likely than men to be attracted to MA for weight loss and to control symptoms of depression. Over 70% of MA-dependent women report histories of physical and sexual abuse and are more likely than men to present for treatment with greater psychological distress. MA has been a popular drug among MSM since the 1980s. MSM report using MA to combat feelings of loneliness and isolation and to promote sexual desire and sexual behavior.[37,38] In addition to the appeal of its sexual effects, MA serves as a coping tool for many MSM with HIV or AIDS. MSM with HIV report using MA to manage symptoms of HIV disease, such as fatigue, or to remedy HIV-related "burn out" and depression.[37]

MA's dramatic effect on sexual desire and sexual behavior has been a major public health concern, as it has been associated with increasing risk for transmission of HIV.[37,39] Sexual practices associated with MA use include increased numbers of casual and anonymous sexual partners, increased anal intercourse, decreased condom use, sex trading, group sex, and more frequent and longer episodes of sexual activity.[40–42] The multicenter AIDS cohort study and several other studies found a high correlation between MA use and HIV seroconversion[40] and other sexually transmitted infections, such as syphilis, gonorrhea, and hepatitis.[43–45] Treatment of MA dependence may be one of the most effective strategies in reducing the spread of HIV and other associated sexually transmitted infections.

Pharmacotherapy treatments

Until date, there is limited literature on evidence-based pharmacological treatment approaches for MA withdrawal. Antidepressants and anxiolytics may be used to ameliorate depressive and anxiety symptoms, though research suggests only limited benefits of antidepressants in reducing withdrawal symptoms.[46] Neuroleptics may be used to treat MA-induced psychotic symptoms in the context of intoxication or recent use,[47] and a recent study demonstrated the equivalent efficacy of Olanzapine (Zyprexa), an atypical neuroleptic, and haloperidol (Haldol), atypical neuroleptic, in improving psychotic symptoms related to amphetamine use.[48]

The research literature lacks substantiation of efficacy of any medication as a treatment for MA dependence. Past work has failed to determine the efficacy of compounds such as selegiline (Eldepryl), sertraline (Zoloft), gabapentin (Neurontin), rivastigmine (Exelon), risperidone (Risperdal), ondansetron (Zofran),[49] and Abilify (Aripiprazole)[50] as potential treatments for MA dependence.

Medication development for MA addiction generally strives to address deficits caused by MA use or associated with withdrawal. The target of therapeutic development has focused on initiation of abstinence and prevention of relapse. Bupropion (Wellbutrin), modafinil (Provigil), naltrexone, mirtazapine (Remeron), and baclofen (Lioresal) have exhibited limited utility in treating MA addiction, especially in conjunction with behavioral therapy. Other medications (e.g., lobeline, vigabatrin) are under consideration, but evidence for efficacy is lacking and the scant data that do exist contain no information regarding the suitability for various populations. Also of interest is a "replacement" or "substitution" approach with other stimulants such as methylphenidate,[51,52] akin to methadone for opioid addiction. As with methadone, however, such a pharmacotherapy enables the patient to rehabilitate in other life areas, but does not lead to near-term abstinence from stimulants. There is at least one clinical trial in Iran, which recently compared aripiprazole with risperidone for treatment of MA induced psychosis, based on findings of this study risperidone is better choice for patients with positive psychosis symptoms and vice versa aripiprazole is better for patients with negative psychosis symptoms.[53]

Matrix model of cognitive behavioral therapy (CBT): The matrix model incorporates principles of CBT in individual and group settings, family education, motivational interviewing, and behavioral therapy that employ CBT principles.

This manualized therapy has been proven effective in reducing MA use during the 16-week application of the intervention, in comparison to a "treatment as usual" condition.[54–57] The matrix model has been evaluated as a stand-alone treatment for subgroups of MA abusers (e.g., gay and bisexual men and heterosexuals) and as the behavioral treatment platform in pharmacotherapy trials for MA dependence.[57]

Contingency management (CM) therapy for treatment of stimulant use disorders employs principles of reinforcement for demonstration of desired behaviors. Drug use can be brought under control if desired behaviors that replace or compete with drug use are followed by rewards to increase the frequency of these behaviors. Thus, CM combined with a pharmacotherapy, such as modafinil that potentially enhances cognition or restores memory/learning processes impacted by MA dependence could be a potent approach. CM and CBT have been assessed for comparative effectiveness in treating stimulant dependence with a group of cocaine- and MA-dependent individuals-participants who received CM were retained in treatment significantly longer than those who received only CBT and they provided more stimulant-negative urine samples.[55]

Another approach is empowering patients and their families by empower based interventions which could be effective for Iranian patients.[56]

Harm reduction

Some MA users who do not want treatment and cannot stop using MA should be considered as a target group of harm reduction services.[58] Harms of MA use includes:

- Direct medical harms such as cardiovascular disease, pulmonary problems, liver disease, strokes, pregnancy complications, neurological/mental complications, and dental complications.
- Indirect medical harms such as HIV and hepatitis B and/or C because increase in high risk sex behaviors and sharing behaviors.[59–62] Even in non-injecting MA users we can see an increase in the rate of hepatitis C because of pipe sharing.[63]
- Indirect social harms such as increase in minor and major crimes[64,65] and violence.[66,67]

Current harm reduction strategies have been established in the context of heroin injecting drug users (IDUs) and have been shown to be effective for controlling HIV epidemic among these opiate using IDUs.[68] Many of the harm reduction strategies developed for IDUs are likely to be useful for injecting MA users. Needle exchange has been shown to be an effective harm reduction strategy with opiate injectors, but there is evidence that MA injectors prefer to take, but avoid engagement with service providers resulting in less opportunity for patient education.[69] Establishment of harm reduction facilities that are accepting, non-stigmatizing and provide food, and support services could be useful for engaging MA users into a safe environment. Furthermore, there is some evidence that the availability of smoking equipment such as pipes may provide some benefit in reducing injection use.

MA use increases sexual risk behaviors[61] Condom promotion programs as well as safer sex education and safer sex negotiation for both male and female MA users can be part of harm reduction activities for MA users. In countries such as Iran that already have established harm reduction strategies for IDUs, MA harm reduction activities should be integrated with current activities to expand the impact of the programs. Consideration should be given to employing communication tools including mobile phones, virtual social networks, and text messaging to expand outreach activities.[70–72]

Conclusion

MA, a drug that is widely used in many parts of the world, produces significant acute and chronic medical and psychiatric conditions. Currently, there are no medications that have shown evidence of efficacy in the treatment of MA dependence. Several behavioral treatments have been shown to reduce MA use, but additional treatments are needed to provide a sufficient set of clinical tools to adequately treat the majority of MA-dependent individuals. The development of effective treatments that can reduce the use of MA as well as its consequent medical and psychiatric comorbidities is an important priority for future research. Integration of MA harm reduction strategies in current harm reduction programs as well as tailoring new innovative methods for better access to harm reduction assistance for both

injecting and non-injecting MA users should be considered as a priority. Iran and many other developing countries in the region are newly facing problems with MA, rapidly and widely, it is highly recommended that responsible authorities and scientific communities try to establish appropriate and effective response for prevention, treatment and harm reduction services, which specially should be tailored considering local resources and characteristics.

Conflict of Interests

The Authors have no conflict of interest.

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پژوهش‌های اخیر درباره متامفتامین: همه‌گیر شناسی، اثرات جسمی و روانی، درمان و تلاش در جهت کاهش آسیب

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مقاله مروری

چکیده

مقدمه: متامفتامین (با نام مصطلح شیشه در ایران) ماده روان‌گردانی است که در دنیا به گستردگی در حال استفاده می‌باشد و در ایران نیز نزدیک به یک دهه است که در دسترس عموم مصرف کنندگان قرار گرفته است و شیوع مصرف بسیار بالایی دارد. به همین دلیل شناخت بیشتر آن موردنیاز درمانگران و پژوهشگران این حیطه می‌باشد.

بحث: مصرف متامفتامین عوارض متعددی بر سیستم عصبی مرکزی به جای می‌گذارد که بعضی قابل برگشت و بعضی برای مدت‌های طولانی گریبان‌گیر فرد می‌باشد. این ماده با توانایی تحریک مدار پاداش مغزی، تجربیاتی برای فرد مصرف کننده به وجود می‌آورد که وی را به شدت به مصرف مکرر آن ترغیب می‌کند و در نهایت این فرایند می‌تواند به اعتیاد و وابستگی ختم گردد. شیوه مصرف تدخینی یا تزریقی این ماده باعث می‌شود تا تأثیرات آن بلافاصله بعد از مصرف در فرد مصرف کننده حس شود و این امر باعث افزایش احتمال اعتیادآوری آن و عوارض جسمی و روان‌پزشکی بیشتری می‌گردد. تاکنون درمان دارویی مؤثری برای وابستگی به متامفتامین در دسترس نیست. اگرچه در این حیطه پژوهش‌های گسترده‌ای در جریان می‌باشد. چندین مدل درمان رفتاری تأثیر خود را در کاهش میزان مصرف متامفتامین نشان داده‌اند، اما نیاز به درمان‌های بهتری در این زمینه احساس می‌گردد.

نتیجه‌گیری: باید راهبردهای کاهش آسیب برای مصرف کنندگانی که به دنبال قطع مصرف متامفتامین نیستند مدنظر قرار گیرد تا احتمال بروز HIV (Human immunodeficiency virus) و دیگر آسیب‌های جسمی در این گروه کاهش یابد. دامنه پژوهش در این حیطه با توجه به نیاز به درمان‌های مؤثر دارویی (به عنوان یکی از مهم‌ترین اولویت‌ها) بسیار گسترده می‌باشد.

واژگان کلیدی: متامفتامین، همه‌گیر شناسی، عوارض جانبی، درمان، کاهش آسیب، ایران

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Methamphetamine-Associated Psychosis and Treatment With Haloperidol and Risperidone: A Pilot Study

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Abstract

Background: Different studies have suggested that antipsychotic medications of the first generation have better effectiveness for the treatment of psychotic symptoms compared with antipsychotic medications of the second generation.
Objectives: The current study was the first pilot study in Iran that compared Haloperidol with Risperidone in the treatment of positive symptoms of psychosis among a group of methamphetamine-dependent patients.
Materials and Methods: This randomized clinical trial was designed and conducted in 2012. Overall, 44 patients who met the diagnostic and statistical manual of mental disorders, fourth edition-text revised (DSM.IV-TR) criteria for methamphetamine-associated psychosis (MAP) and were hospitalized at Razi psychiatric hospital in Tehran were selected. Patients (1: 1) were randomly divided to two groups. Overall, 22 subjects received Haloperidol (5 - 20 mg) and 22 subjects received Risperidone (2 - 8 mg). All subjects were assessed at baseline, during three consecutive weeks of treatment and one week after treatment (i.e., follow-up). Scale of assessment of positive symptoms (SAPS) was completed for each subject.
Results: The study findings indicated that both Haloperidol (< 0.05) and Risperidone (< 0.05) were similarly applicable in the treatment of MAP but no differential effectiveness was found between the two medications. The treatment effects of both medications increased in the first two weeks of treatment and remained stable in the second two weeks.
Conclusions: Risperidone and Haloperidol are two effective antipsychotic medications for the treatment of positive symptoms of MAP but other aspects of these two neuroleptic medications such as the long-term treatment effects should be studied. Further studies with more samples and longer follow-ups are suggested.

Keywords: Haloperidol, Methamphetamine, Psychosis, Risperidone, Treatment

1. Background

As an addictive psychostimulant drug, methamphetamine use is a new health concern in Iran but a few studies have targeted treating methamphetamine-associated psychosis (MAP) with antipsychotic medications in Iran and around the world (1-25).

2. Objectives

In the recent years, MAP has impacted the healthcare system of Iran (2).

3. Materials and Methods

3.1. Participants and Eligibility Criteria

The current pilot study had a randomized clinical trial design. The study was conducted in 2012. Patients who were hospitalized at Razi psychiatric hospital in Tehran and at the same time, were diagnosed with MAP based on the diagnostic and statistical manual of mental disorders, fourth edition-text revised (DSM.IV-TR) criteria, were eligible to enter the study. Other inclusion criteria included age range of 18 - 60 years, and the chronicity and severity of positive symptoms. Exclusion criteria included meeting Axis I psychiatric comorbidity especially Schizophrenia, co-use of other types of substances like opioids within the past month prior to recruitment, current neurological disorders, mental retardation, and taking medications such as other antipsychotic and Benzodiazepines before starting the study.

3.2. Study Measures

Details of baseline demographics such as gender, age, history of psychiatric disorders, history of drug use and

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current methamphetamine use were recorded using a checklist. By the assistance of the psychiatrist of Razi hospital, the clinical files of the patients were also reviewed to complete the data collection. The Persian validated version of the scale of assessment of positive symptoms (SAPS) was completed for each patient to assess positive symptoms of psychosis amongst the patients. It should be noted that we did not use the scale of assessment of negative symptoms (SANS) to assess negative symptoms of psychosis among our sample because negative symptoms do not emerge in MAP.

Scale of assessment of positive symptoms was developed by Andersen to assess positive symptoms of psychosis. The assessed positive symptoms include hallucinations, delusions, deviant behaviors and disrupted concrete thinking. Scale of assessment of positive symptoms includes 30 questions. Each question has six scores ranging from 0 to 5. The total scores range between 0 and 150 (26). It has high reliability and validity to assess negative symptoms of psychosis. Internal consistency of the Persian validated version was 83%, and pre-test and posttest reliability was 88% (25). In this study, internal reliabilities via Cronbach alpha coefficients for positive symptoms were 92% indicating high reliability to meet the study aims.

3.3. Ethical Considerations

Participation was confidential and voluntary. Consent forms were obtained from the caregivers. The protocol of the study was approved by the ethical committee of University of Social Welfare and Rehabilitation Sciences in Tehran, Iran.

3.4. Study Procedure

After meeting all eligibility criteria and obtaining consent forms, 44 patients with current psychiatric diagnosis of MAP were recruited. Patients were randomly divided to two groups based on a given random code including 22 patients in the Haloperidol group and 22 patients in the Risperidone group. This was done by a well-trained psychiatrist. Group 1 received Haloperidol (5 to 20 mg, per day, starting with 5 to 10 mg per day and raised gradually every three to four days up to 20 mg according to the symptoms) and group 2 received Risperidone (2 - 8 mg, per day, starting with 2 to 4 mg per day and raised gradually every three to four days up to 8 mg according to the symptoms) at baseline and for three consecutive weeks. Patients were followed after one week. Scale of Assessment of Positive Symptoms was completed on a weekly basis for each patient. The duration of study was one month because studies showed that the required time for showing treatment failure with antipsychotic medications was four to six weeks. Furthermore, based on the DSM.IV-TR criteria, the psychiatric diagnosis of MAP will be wrong if it takes more than one month. During one month, symptoms of MAP were assessed weekly. In this study, assessment of SAPS included hallucinations, delusions, deviant behaviors positive concrete thinking and the total score of SAPS.

3.5. Data Analysis

Data was analyzed by performing descriptive methods of statistics, independent t-test and variance analysis with repeated measures, using the SPSS version 19 software.

4. Results

Overall, 54.6% of the subjects were male in the Haloperidol group (group 1) and 86.4% of the subjects were male in the Risperidone group (group 2). The mean age of group 1 was 35.3 $\pm$ 7.9 years and the mean age of group 2 was 34.6 $\pm$ 7.9 years. Overall, 68% of the subjects in group 1 and 82% of subjects in group 2 were currently single. In total, 72.7% of the subjects in group 1 and 59.1% of the subjects in group 2 were unemployed (See Table 1).

The table below shows the mean scores of the two groups in hallucination. As Table 2 shows the mean scores of hallucination in the two groups were reduced from 13.5 (SD = 6.3) in the Haloperidol group and 15 (SD = 4.9) in the Risperidone group at baseline to 0.14 (SD = 0.4) and 0.27 (SD = 0.76) on the third week of treatment, respectively. The mean scores of delusion in the two groups were reduced from 17 (SD = 7.8) in the Haloperidol group and 15.7 (SD = 7.4) in the Risperidone group at baseline to 0.14 (SD = 0.64) and 0.73 (SD = 1.5) on the third week of treatment, respectively. The P value for all items was < 0.05, which was significant (See Table 2).

The table below shows the mean scores of the two groups in bizarre behavior. As the table shows the mean scores of bizarre behavior in the two groups was reduced from 8.5 (SD = 4) in the Haloperidol group and 7.7 (SD = 3.3) in the Risperidone group at baseline to 0.00 (SD = 0) and 0.27 (SD = 0.63) on the third week of treatment, respectively. The P value for all items was < 0.05, which was significant (See Table 3).

The mean scores of hallucination in the Haloperidol group and Risperidone group were (13.5 (SD = 6.3) and 15.09 (SD = 4.9), t = 0.8), respectively. The mean scores of delusion in Haloperidol group and Risperidone group were 17.0 (SD = 7.8) and 15.7 (SD = 7.0), t = 0.5), respectively. The mean scores of bizarre behavior in the Haloperidol group and Risperidone group were 8.5 (SD = 4.0) and 7.6 ((SD = 3.3), t = 0.7), respectively. The mean scores of concrete thinking in the Haloperidol group and Risperidone group were 5.7 (SD = 2.8) and 8.9 ((SD = 4.0), t = 3.0), respectively.

Table 1. Details of Demographics Among the Patients in the Two Groups (n = 44)

	Group 1	Group 2	P Value
Gender			
Male	12 (54.6)	19 (86.4)	0.03
Female	10 (45.4)	3 (13.6)	0.06
Mean age, y	35.3 (SD ± 7.9)	34.6 (SD ± 7.9)	
Education status			
Less than 12 years	19 (86.4)	20 (90.9)	
12 years	3 (13.6)	2 (9.1)	
Age range, y			
21 - 33	10 (45.4)	9 (41)	0.09
34 - 46	10 (45.4)	11 (50)	0.08
47 - 59	2 (10.2)	2 (9)	0.02
Marital status			
Currently single	7 (31.2)	4 (18)	
Currently married	6 (27.3)	9 (40.9)	0.08
Job status			
Currently has a job	15 (68.2)	18 (82)	
Currently unemployed	16 (72.7)	13 (59.1)	0.065
Duration of current hospitalization (days)	3 (SD ±3.9)	2 (SD ±5.8)	
Duration of methamphetamine use (Months)	7(SD ±4.7)	9 (SD ±6.9)	0.08

Table 2. Mean Scores of Hallucination/Delusion (n = 44)

Psychiatric Medication, n = 22	Treatment Stage	Mean Scores /SD
Haloperidol	Baseline/hallucination	13.5 (6.3)
	Week 1	3 (4.1)
	Week 2	0.91 (2.3)
	Week 3	0.14 (0.4)
	Week 4	0.00 (0)
Risperidone	Baseline	15 (4.9)
	Week 1	4 (4.3)
	Week 2	0.64 (1.4)
	Week 3	0.27 (0.76)
	Week 4	0
Haloperidol	Baseline/Delusion	17 (7.8)
	Week 1	5 (5.3)
	Week 2	0.86 (2.2)
	Week 3	0.14 (0.64)
	Week 4	0.00 (0)
Risperidone	Baseline	15.7 (7.4)
	Week 1	6.2 (6.6)
	Week 2	2.6 (4.7)
	Week 3	0.73 (1.5)
	Week 4	0.00 (0)

The mean scores of psychotic symptoms in the Haloperidol group and Risperidone group were 45.7 (SD = 14.4) and 45.4 ((SD = 12.2), t = 0.42), respectively. Although, the mean scores of the two groups improved in hallucination, delusion, bizarre behavior, concrete thinking and psychotic symptoms yet there was not significant difference between the two groups. In this study, the P value for all items was < 0.05, which was significant (See Table 4).

As Table 3 shows the mean scores of concrete thinking in the two groups were reduced from 5.7 (SD = 2.8) in the Haloperidol group and 8.9 (SD = 4.0) in the Risperidone group at baseline to 0.05 (SD = 0.21) and 0.36 (SD = 0.72) on the third week of treatment, respectively. The P value for all items was < 0.05, which was significant (See Table 3).

As Table 3 shows the mean scores of psychotic symptoms in the two groups were reduced ranging from 45.7 (SD = 14.4) in the Haloperidol group to 47.4 (SD = 12.2) in the Risperidone group at baseline and from 0.27 (SD = 10.07) to 1.6 (SD = 2.9) on third week of treatment, respectively (See Table 3).

5. Discussion

Over the past decade, a growing body of evidence suggests that second-generation antipsychotics such as Risperidone are effective in the treatment of patients with psychosis (27). Current research evidence strongly suggests a relationship between methamphetamine use and the development of acute psychosis. First, early studies demonstrated that methamphetamine could trigger acute psychosis in healthy individuals (28).

The positive symptoms of methamphetamine psychosis are similar to those of paranoid schizophrenia, consisting mainly of delusions and hallucinations. The recurrent nature of methamphetamine psychosis is also suggested as another apparent similarity, as recurring methamphetamine psychosis could be similar to schizophrenia (29).

The current pilot study is one of the few studies in Iran that considered MA psychosis treatment with Haloperidol

Table 3. Mean Scores of Bizarre Behaviors/Concrete Thinking (n = 44)

Psychiatric Medication, n = 22	Treatment Stage	Mean Scores/SD
Haloperidol	Baseline/bizarre behaviors	8.5 (4)
	Week 1	0.5 (1.3)
	Week 2	0.1 (0.4)
	Week 3	0
	Week 4	0
Risperidone	Baseline	7.7 (3.3)
	Week 1	1.7 (2.5)
	Week 2	0.4 (0.9)
	Week 3	0.2 (0.6)
	Week 4	0. 5 (0.2)
Haloperidol	Baseline/Concrete Thinking	5.7 (2.8)
	Week 1	1.3 (1.2)
	Week 2	0.2 (0.5)
	Week 3	0.5 (0.2)
	Week 4	0
Risperidone	Baseline	8.9 (4.0)
	Week 1	2.6 (3.1)
	Week 2	1.09 (1.5)
	Week 3	0.3 (0.7)
	Week 4	0
Haloperidol	Baseline/Psychotic Symptoms	45.7 (14.4)
	Week 1	10.05 (8.9)
	Week 2	2.05 (4.7)
	Week 3	0.27 (1.07)
	Week 4	0
Risperidone	Baseline	47.4 (12.2)
	Week 1	14.5 (13.9)
	Week 2	2.6 (4.5)
	Week 3	1.6 (2.9)
	Week 4	0

and Risperidone among a group of patients, who were hospitalized at Razi psychiatric hospital. A few studies from Iran have targeted treating MAP. The study findings suggested that both Haloperidol and Risperidone were effective for the treatment of MAP yet there was no significant difference between the two antipsychotic medications. A few studies in other countries have addressed the treatment of MAP with antipsychotic medications. The findings of the current study are in contrast with the study findings of Green et al. (2002) (30), who found that Haloperidol was more effective in treating psychosis in comparison with Risperidone.

In another study, it was found that making a treatment transition from Haloperidol to Risperidone among Schizophrenic patients reduced the scores of subscales of positive, negative and general psychosis symptoms (31). Zhang et al. (2001) (32) found that the general symptoms of psychosis in the Risperidone group were significantly improved compared with the Haloperidol group. A study found that Risperidone was superior in the treatment of symptoms of psychosis compared with Haloperidol (33).

The reported changes in these studies can be the result of several factors. First, the dose of use may impact the treatment effects. In fact, there is still no agreement on the dose required to treat positive symptoms of MAP, especially for Risperidone. There are no studies that have examined the best dosage. There is only evidence that higher doses of antipsychotic medications have better effectiveness compared with lower ones. Further studies of this issue are still required.

It should be noted that positive symptoms of MAP are associated with considerable health service utilization and increased psychiatric symptoms over time (34). Little is known about the pharmacological therapies of patients with MAP in Iran. In addition, the most effective regime for stabilizing patients with MAP still needs to be studied in Iran. Methamphetamine users are vulnerable to MAP, either as a result of exacerbation of symptoms of underlying psychotic disorders (35) or emerging new psychotic symptoms during intoxication and withdrawal stages (36); recurrence can occur in response to psychological stressors even in the absence of methamphetamine use (37).

Recently, however, the picture of success for these antipsychotic medications has become somewhat vague. Patients diagnosed with positive symptoms of MAP should be monitored more closely, in particular for signs of a chronic development.

5.1. Limitations and Suggestions

The current study also had some limitations as follows: the study sample was limited to only one psychiatric center. Therefore, data generalization is difficult. Because of a number of problems such as difficulty in sample recruitment, the sample size was small. Further studies with more representative numbers of samples are suggested. Because of psychiatric treatment of patients, it was difficult to have further follow-ups. Therefore, designing and conducting research studies with more follow-up sessions are suggested. In this study, we compared the therapeutic effectiveness of Haloperidol with Risperidone in the treatment of MAP yet further studies with Placebo groups are

Table 4. The Differences Between the Two Groups in Treatment of Positive Symptoms of Methamphetamine-Associated Psychosis (n = 44)

Group	PS	Mean/SD	F	Mean/SD	df	t	P
Haloperidol Risperidone	Hallucination	13.5 (6.3) (15.0 (4.9)	0.32	1.05 (1.7)	42	0.8	0. 22
Haloperidol Risperidone	Delusion	17.0 (7.8) 15.7 (7.0)	0.15	1.27 (2.3)	42	0.5	0.22
Haloperidol Risperidone	Bizzarre behaviors	8.5 (4.0) 7.6 (3.3)	0.48	0.48 (0.8)	12	0.7	0.12
Haloperidol Risperidone	Concrete thinking	5.7 (2.8) 8.9 (4.0)	0.47	(3.18 (1.04)	42	3.3	0.12
Haloperidol Risperidone	Psychotic symtopms	(45.7) (14.4) (45.4 (12.2)	1.22	1.73 (0.67)	42	0.4	0.11

Abbreviation: PS, Psychotic symptoms.

still suggested. However, the current study is one the few studies in Western Asia, especially the Persian Gulf region, which targeted treating MAP with antipsychotic medication.

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Footnotes

Authors' Contribution: Mercedeh Samiei, Mohammad Vahidi and Reza Daneshmand designed the study. Mohammad Vahidi, Azadeh Yaraghchi and Omid Rezaee conducted the study. Reza Daneshmand performed the data analysis. All authors contributed to writing the manuscript and reading and approving the final version.

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Bupropion Reduces Methamphetamine-Induced Subjective Effects and Cue-Induced Craving

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Bupropion is an antidepressant with stimulant properties, which inhibits the reuptake of dopamine (DA) and norepinepherine, and is purported to enhance DA neurotransmission. Bupropion is considered an appealing candidate medication for the treatment of methamphetamine dependence. The current laboratory study was set forth to assess the impact of bupropion treatment on the subjective effects produced by methamphetamine in the laboratory. We also assessed the effects of bupropion treatment on craving elicited by exposure to videotaped methamphetamine cues. A total of 26 participants were enrolled and 20 completed the entire study ($n = 10$ placebo and $n = 10$ bupropion, parallel groups design). Bupropion treatment was associated with reduced ratings of 'any drug effect' ($p < 0.02$), and 'high' ($p < 0.02$) following methamphetamine administration. There was also a significant bupropion-by-cue exposure interaction on General Craving Scale total score ($p < 0.002$), and on the Behavioral Intention subscale ($p < 0.001$). Overall, the data reveal that bupropion reduced acute methamphetamine-induced subjective effects and reduced cue-induced craving. Importantly, these data provide a rationale for the evaluation of bupropion in the treatment of methamphetamine dependence.
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INTRODUCTION

Methamphetamine dependence directly or indirectly affects millions of Americans, and despite the efficacy of current treatments for some patients, relapse remains a significant problem (Huber *et al*, 1997; Rawson *et al*, 1999, 2004; Shoptaw *et al*, 1994). These studies, along with many others, underscore the challenge inherent in providing effective treatment to methamphetamine users.

A number of factors are thought to contribute to relapse, including drug availability and exposure to drug cues. Drug cues ('triggers') include people, places, and things associated with drug use. This has been studied more fully in opiate and cocaine dependence, although similar considerations are likely to apply to dependence on methamphetamine (Ehrman *et al*, 1992; O'Brien *et al*, 1976).

There have been sustained and partly successful efforts to develop medication treatments for drug abuse disorders (de Lima *et al*, 2002; Garbutt *et al*, 1999; Mattick *et al*, 2002; Sofuoglu and Kosten, 2005), although fewer medications have been studied in randomized clinical trials for the treatment of methamphetamine dependence (Galloway *et al*, 1994, 1996; Huber *et al*, 2000).

Bupropion is an attractive candidate medication for the treatment of methamphetamine dependence for several reasons. Bupropion is an antidepressant with stimulant properties (Stahl *et al*, 2004) that is effective for the treatment of nicotine dependence (Richmond and Zwar, 2003). In a clinical trial of bupropion for cocaine dependence (Margolin *et al*, 1995), an exploratory analysis suggested that patients with greater levels of depression may have benefited the most. Clinically, acute abstinence from methamphetamine in chronic users is associated with depression and impaired concentration (Newton *et al*, 2004). These symptoms may be due to methamphetamine-induced neuroadaptations in presynaptic DA neurons manifest as reduced striatal DA availability (McCann *et al*, 1998; Sekine *et al*, 2003; Volkow *et al*, 2001; Wilson *et al*,

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1996). Bupropion inhibits the reuptake of DA and enhances residual DA neurotransmission, effects that may ameliorate methamphetamine abstinence symptoms. The current laboratory study was designed to assess the impact of bupropion treatment on the subjective effects produced by methamphetamine and to assess the effects of bupropion treatment on craving elicited by exposure to methamphetamine cues.

MATERIALS AND METHODS

Subjects

In total, 26 participants were enrolled and 20 completed the entire study ($n = 10$ placebo and $n = 10$ bupropion, parallel groups design). Participants were recruited through advertisements and were paid for their participation. All met DSM-IV-TR criteria for methamphetamine abuse or dependence and were not seeking treatment at the time of study entry. Other inclusion criteria included being between 18 and 45 years of age, a history of using methamphetamine by the smoked or intravenous (i.v.) route, twice-weekly use of methamphetamine in 4 of the 6 weeks prior to screening, and normal laboratory assessment and vital signs. Exclusion criteria included a history of seizure disorder, head trauma, dependence on other drugs aside from nicotine, prior adverse reaction to methamphetamine, or the presence of any other axis I psychiatric disorder. Serious medical conditions such as heart disease, AIDS, asthma, Parkinson's disease, and other serious medical conditions were also exclusionary. Concomitant use of psychotropic medications or medications interacting with bupropion was not allowed. This study was approved by the institutional review boards at both UCLA and the University of Texas Health Sciences Center at San Antonio (UTHSCSA), and all participants gave informed consent after being fully informed about potential risks of participation.

Study Design

The study was conducted using a double-blind design at UCLA and UTHSCSA. Following admission to the clinical research center (CRC), subjects received a baseline series of i.v. doses of methamphetamine (0, 15, and 30 mg). Subjects received a second identical series of methamphetamine doses 6 days after initiation of twice-daily oral placebo or bupropion treatment. The order of the methamphetamine 0 and 15 mg administration sessions was randomly assigned, although the 30 mg methamphetamine dose always followed the lower doses (see Study Scheme: Table 1). Thus, the investigators (but, not the participants) were not blinded to the 30 mg methamphetamine dose. Assignment of placebo and bupropion was random, and stratified by site.

Drugs

Commercially available bupropion tablets (150 mg extended-release) were cut in half (due to the large size of the tablet) and encapsulated in gelatin capsules by research pharmacies at each site. The manufacturer provided documentation that these procedures did not affect bioavailability of the bupropion (personal communication to Dr John Roache). Placebo was prepared in a similar manner. A NIDA contractor provided sterile methamphetamine solution for human use and a saline solution of equal volume and appearance was used as the control. An IND was obtained from the FDA for the use of bupropion and methamphetamine in this study. Methamphetamine was administered over 2 min (between 0900 and 1100 hours on specified infusion days) using an i.v. pump.

Table 1 Summary of i.v. Doses of Methamphetamine Administered at Baseline and 6 Days after Initiation of Twice-Daily Oral Placebo or Bupropion Treatment

Study phase	Session	Study day	Methamphetamine challenge (mg)
Baseline	1	2	0 or 15
Baseline	2	3	0 or 15
Baseline	3	5	30
Treatment	4	18	0 or 15
Treatment	5	19	0 or 15
Treatment	6	22	30

Subjective Measures

Subjective effects data were collected using computerized visual analog rating scales (VAS), the Within Session Rating Scale (WSRS, a craving rating scale), the General Craving Scale (GCS)(Merikle, 1999), the Multiple Choice Questionnaire (MCQ), Brief Psychiatric Rating Scale (BPRS), Adjective Scales, and the Addiction Research Center Inventory (ARCI) (Haertzen, 1965, 1966).

VAS data were collected at 15 min before, and 3, 6, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min following methamphetamine or placebo administration. For the VAS scales, subjects reported the degree to which they feel 'any drug effect', 'high', 'good effects', 'bad effects', 'like methamphetamine', 'desire for methamphetamine', 'depressed', 'anxious', 'stimulated', and 'likely to use' on a continuous scale digitized between 0 and 100. In addition, they were asked to answer the question: 'How much would you pay for this drug'?

Within the first several days of the study, participants rated craving (using the WSRS and the GCS) prior to and following exposure to a neutral cue video consisting of a nature scene. On subsequent days (twice prior to randomization and twice after randomization), participants rated craving prior to and following exposure to a cue video showing actors using drugs. Cueing procedures took place on days that participants could potentially receive 15 mg methamphetamine in order to maintain the salience of the cues. The GCS consists of 59 questions rated on a scale of 1–5, and yields data on several dimensions, including 'behavioral intention', 'physical symptoms', 'positive outcome', 'affect', 'cues affect', and several others.

Participants also completed the MCQ, in which participants complete a series of hypothetical choices between

doses of methamphetamine and varying amounts of money. The crossover point indicated how much participants would pay for a dose of methamphetamine.

The BPRS is a psychiatrist-administered interview that was conducted 60 min after methamphetamine/saline infusion sessions. The BPRS evaluates the severity of subject's psychopathology, including anxiety, depression, and symptoms of schizophrenia. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization.

Adjective Scales consisted rating of 22 adjectives on a scale of 0–4, ranging from 'not at all' to 'extremely', and the ARCI consisted of 49 statements in a true/false format. The BPRS was administered 60 min following methamphetamine administration to detect possible behavioral toxicity (Overall and Gorham, 1962). The Adjective Scales and the ARCI were administered 15 min before and at 30 min after each infusion. The ARCI and Adjective Scale were included to assist interpretation, if needed.

Data Analysis

The primary outcome measures were changes in subjective ratings following administration of i.v. methamphetamine, as compared to placebo. A secondary outcome measure was change in self-reported craving following exposure to a cue video showing actors using drugs. Descriptive statistics for demographic data are presented for all subjects ($n=26$). However, because of the need to balance the mixed repeated measures design, inferential analyses of the primary outcome data were possible only for the 20 completers. Subjective effects data were analyzed using SAS Proc Mixed (Release 8.2). Fixed effects of Bupropion dose (0 or 150 mg), Period (before *vs* after initiation of bupropion/placebo treatment), and Methamphetamine dose (0, 15, or 30 mg) were specified in a factorial design (with repeated measures on Period and Methamphetamine dose). In addition, we also examined the effects of Bupropion and Period on the maximum subjective effects reported following methamphetamine administration, using the baseline response immediately prior to dosing as a covariate. The covariance structure was specified as autoregressive and the empirical option was used to maximize validity of this assumption.

RESULTS

Demographics and Drug Use

A total of 26 participants were enrolled and 20 completed the entire study ($n=10$ placebo and $n=10$ bupropion, parallel groups design). Data are presented as a comparison of patients who dropped from the study *vs* those who completed (Table 2), as well as a comparison of all patients who completed and were treated with either bupropion or placebo (Table 3). No significant differences were noted for these comparisons.

Of completers, the majority were non-Hispanic white (55%), male (65%), and had a mean age of 32.8 ± 8.4 years. The majority of completers met criteria for current methamphetamine dependence or current methamphetamine abuse. In addition to methamphetamine use, the completers reported use of several substances, including nicotine (75%), marijuana (55%), and alcohol (85%), in the past 30 days. Participants had significant past histories of abuse of other drugs, including past cocaine dependence, past alcohol abuse or dependence, and past marijuana abuse or dependence.

Table 2 Participant Demographics and Drug Use Data for Drops and Completers

	Drops ($N=6$)	**Completers ($N=20$)**	**Total ($N=26$)**
Gender, N (%)			
Male	4 (67)	13 (65)	17 (65)
Female	2 (33)	7 (35)	9 (35)
Single major race, N (%)			
White, not Hispanic	4 (67)	11 (55)	26 (58)
Hispanic or Latino	2 (33)	6 (30)	8 (31)
African American or Black	0 (0)	1 (5)	1 (4)
Other	0 (0)	2 (10)	2 (8)
Age (years)			
Mean $\pm$ SD	29.7 ± 6.6	32.8 ± 8.4	32 ± 8

	Drops		**Completers**	
Drug/alcohol use, *N* (%)	**Major drug[a]**	**Any use[b]**	**Major drug**	**Any use**
Alcohol	0 (0)	5 (83)	0 (0)	17 (85)
Heroin	0 (0)	0 (0)	0 (0)	0 (0)
Barbiturates	0 (0)	0 (0)	0 (0)	0 (0)
Sedatives/Hypnotics/Tranqs	0 (0)	1 (17)	0 (0)	1 (5)
Cocaine	0 (0)	2 (33)	1 (5)	4 (20)
Amphetamines	0 (0)	1 (17)	0 (0)	0 (0)
Methamphetamine	6 (100)	6 (100)	18 (90)	20 (100)
Cannabis	0 (0)	4 (67)	0 (0)	11 (55)
Inhalants	0 (0)	0 (0)	0 (0)	1 (5)
Nicotine	0 (0)	6 (100)	0 (0)	15 (75)
More than 1 subs/day	0 (0)	4 (67)	1 (5)	15 (75)

[a]The number and percent of subjects for whom the drug is the major substance use problem.
[b]The number and percent of subjects who reported any use of the substance in the last 30 days.

Subjective Effects

There were significant effects of methamphetamine on all VAS measures other than 'depression'. There were significant interactions between Bupropion (0 *vs* 150 mg) and Period (before *vs* after initiation of treatment) for ratings of 'any drug effect' ($p<0.02$), 'high' ($p<0.02$), and there was a trend for ratings of 'stimulated' ($p<0.07$). For 'any drug', there was a trend for a three-way interaction between Methamphetamine, Bupropion, and Period

Table 3 Participant Demographics and Drug Use Data for Completers Only

	Bupropion ($N=10$)	Placebo ($N=10$)	Total ($N=20$)
Gender, N (%)			
Male	5 (50)	8 (80)	13 (65)
Female	5 (50)	2 (20)	7 (35)
Single major race, N (%)			
White, not Hispanic	6 (60)	5 (50)	11 (55)
Hispanic or Latino	3 (30)	3 (30)	6 (30)
African American or Black	0 (0)	1 (10)	1 (5)
Other	1 (10)	1 (10)	2 (10)
Age (years)			
Mean ± SD	32 ± 10.4	33.5 ± 6.3	32.8 ± 8.4

	Bupropion		Placebo	
Drug/alcohol use, *N* (%)	**Major drug[a]**	**Any use[b]**	**Major drug**	**Any use**
Alcohol	0 (0)	8 (80)	0 (0)	9 (90)
Heroin	0 (0)	0 (0)	0 (0)	0 (0)
Barbiturates	0 (0)	0 (0)	0 (0)	0 (0)
Sedatives/Hypnotics/Tranqs	0 (0)	0 (0)	0 (0)	1 (10)
Cocaine	0 (0)	0 (0)	1 (10)	4 (40)
Amphetamines	0 (0)	0 (0)	0 (0)	0 (0)
Methamphetamine	9 (90)	10 (100)	9 (90)	10 (100)
Cannabis	0 (0)	5 (50)	0 (0)	6 (60)
Inhalants	0 (0)	1 (10)	0 (0)	0 (0)
Nicotine	0 (0)	8 (80)	0 (0)	7 (70)
More than one subs/day	1 (10)	6 (60)	0 (0)	9 (90)

[a]The number and percent of subjects for whom the drug is the major substance use problem.
[b]The number and percent of subjects who reported any use of the substance in the last 30 days.

($p<0.08$). This indicated that during the medication treatment phase of the study, volunteers receiving bupropion reported reduced responses on these measures compared to those receiving placebo. In addition, there was a trend for a Bupropion by Period interaction ($p<0.10$) for 'likely to use' and 'desire'. There were significant Bupropion by Methamphetamine interactions for both 'desire' and 'likely to use' scores ($p<0.05$). In both cases, patients receiving placebo showed higher ratings following the 30 mg dose of MA, as compared to the 15 mg dose. Of interest, patients receiving bupropion did not show this dose-related increase, although the effects of Period were not significant. There were no Bupropion effects on 'good effects', 'bad effects', 'liking', 'depression', or 'anxious' scores. In addition, there were no Bupropion effects on the 'pay for the drug' rating following methamphetamine administration. There was no Bupropion effect on responses on the MCQ.

The analyses were repeated using the maximum effect on each rating scale. Very similar results were obtained. Specifically, 'any drug effect' and 'high' remained significant and the three-way interaction for 'any drug effect' became significant, as did the two-way interaction (Bupropion and Period) for 'stimulated'.

For simplicity, and to highlight the most important findings, time-course data from the Treatment phase are shown for 'Any Drug' (Figure 1), 'High' (Figure 2), and 'Stimulated' (Figure 3).

Craving

Exposure to the neutral cue produced minimal, nonsignificant changes in craving ratings. Before initiation of bupropion/placebo treatment, there were no significant Bupropion by cue exposure (before/after) interaction effects. This indicated that the groups did not differ in the magnitude of cue-induced craving at before initiation of active treatment. Following initiation of bupropion/placebo treatment, there were significant Bupropion by cue exposure (before/after) interactions in GCS Total Score ($p<0.002$) and in the Behavioral Intention subscale of the GCS ($p<0.001$). This indicated that treatment with bupropion, compared to placebo, was associated with significantly reduced cue-induced craving (Figure 4). Similar results were obtained for WSRS 'likely to use'. There was a significant Bupropion by Period by cue exposure interaction ($p<0.02$), indicating that during active treatment ratings on this scale were lower. There were no significant effects of bupropion treatment on the WSRS 'feel like using' scores. In general, GCS total scores and scores on each of the subscales were greater prior to randomization, and declined thereafter, possibly indicating that hospitalization, by removing participants from their usual cue-rich environments, reduced cue reactivity.

ARCI, BPRS, and Adjective Scales

Among the ARCI subscales, the pentobarbital–chlorpromazine–alcohol group (PCAG) subscale scores (reflecting sedative effects) decreased with increasing methamphetamine dose, whereas scores on the remaining subscales increased with increasing methamphetamine dose. The only significant Bupropion by Period interaction was seen for the LSD subscale, for which there was a three-way interaction between Bupropion, Period, and Methamphetamine dose ($p<0.05$). Among the Adjective Scales, significant ($p<0.05$) Bupropion by Period interactions were found for 'tremor', 'fidgety', and 'nervous'. Mean values for 'tremor' were low in both groups, reducing the implications of the statistical findings. For the 'fidgety' and 'nervous' ratings, bupropion reduced effects of methamphetamine on these measures during the active medication phase.

BPRS ratings were greater than mild on only 25 of approximately 3215 rating events. Ratings other than mild were more common after 30 mg methamphetamine than after 15 or 0 mg. In all, 12 of the 25 ratings of greater than mild occurred following randomization, and there was no effect of Bupropion treatment on the BPRS ratings.

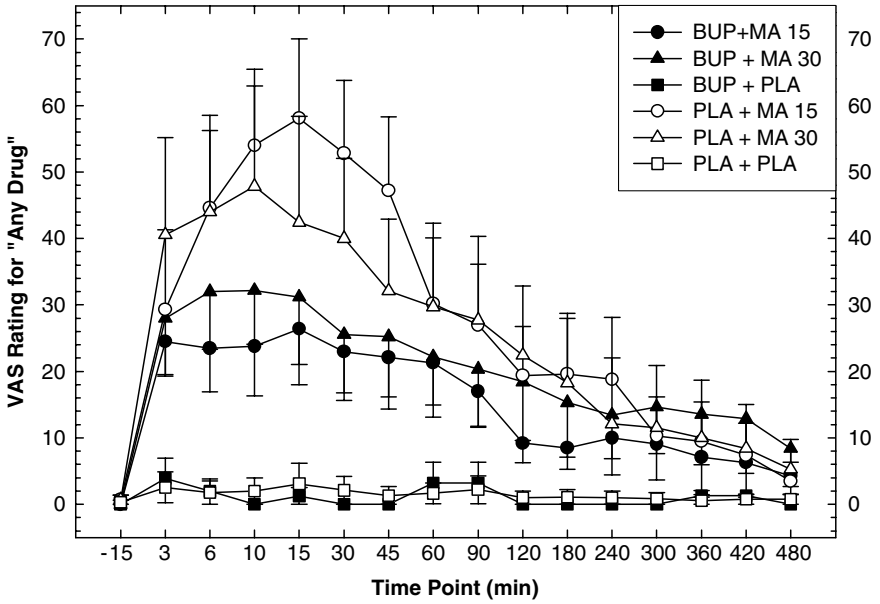
BUP+MA 15
BUP + MA 30
BUP + PLA
PLA + MA 15
PLA + MA 30
PLA + PLA
VAS Rating for "Any Drug"
Time Point (min)
-15 3 6 10 15 30 45 60 90 120 180 240 300 360 420 480
0 10 20 30 40 50 60 70

Figure 1 Ratings for 'any drug' Effects (mean ± SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

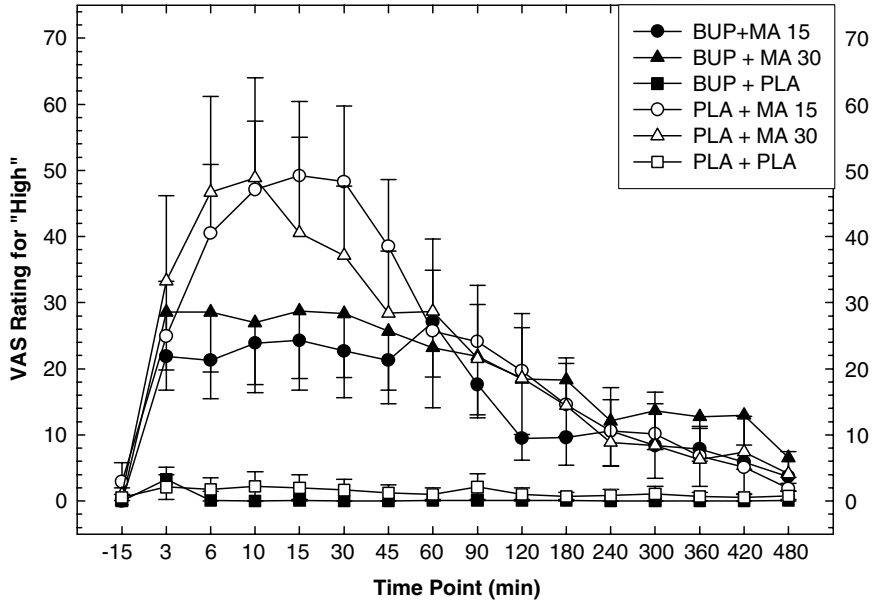

Figure 2 Ratings for 'high' (mean ± SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

DISCUSSION

This group of methamphetamine using volunteers tolerated administration of methamphetamine during treatment with bupropion with no evidence that bupropion enhanced the effects of methamphetamine, or produced behavioral toxicity. Adverse events observed in this study were minor, with both active and placebo groups reporting similar magnitude and severity of events. In fact, bupropion treatment tended to blunt the cardiovascular effects of experimentally administered methamphetamine, with this effect reaching statistical significance for heart rate (Newton *et al*, 2005).

BPRS assessment was included to screen for behavioral toxicity of methamphetamine and to determine if bupropion treatment altered these responses. Very little evidence for behavioral toxicity (eg agitation or psychosis) emerged following administration of methamphetamine, and bupropion treatment did not significantly alter these responses.

Of particular interest, bupropion treatment was associated with reduced 'any drug' and 'high' ratings following methamphetamine administration. Ratings of 'high' and increased scores on ARCI subscales have been associated with abuse liability (Fischman and Foltin, 1991). Bupropion reduced several drug-related subjective effects and did not

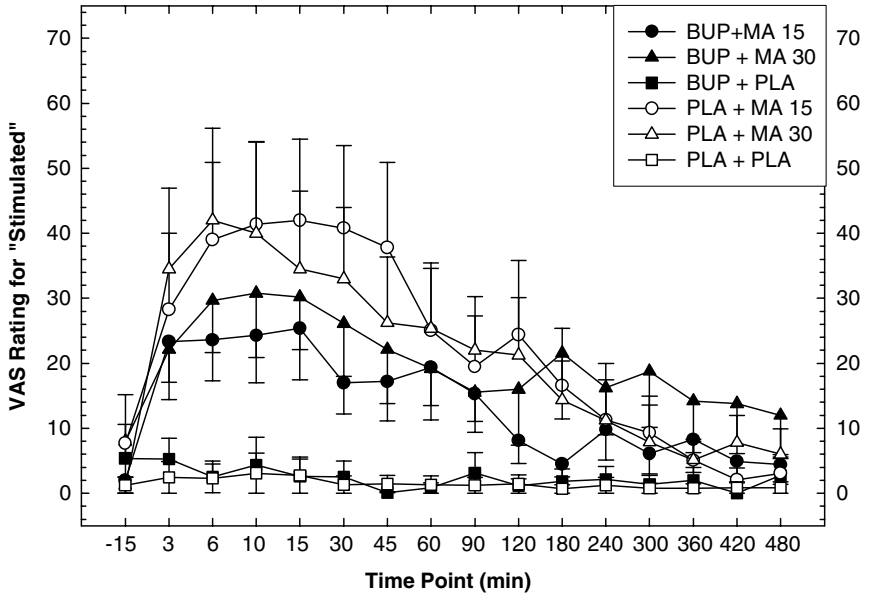
BUP+MA 15
BUP + MA 30
BUP + PLA
PLA + MA 15
PLA + MA 30
PLA + PLA
VAS Rating for "Stimulated"
Time Point (min)
-15 3 6 10 15 30 45 60 90 120 180 240 300 360 420 480
0 10 20 30 40 50 60 70

Figure 3 Ratings for 'stimulated' (mean ± SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

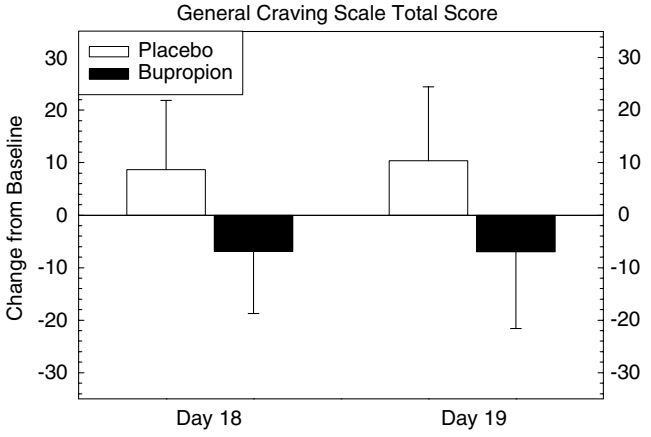

Figure 4 Effects of cue exposure on craving (mean ± SEM). Bupropion treatment (filled bars) significantly reduced cue-induced changes in craving, as compared to effects observed in patients treated with placebo (open bars).

increase ARCI ratings, suggesting that bupropion treatment did not increase the abuse liability of methamphetamine. Instead, bupropion treatment reduced 'any drug' and 'high' ratings, suggesting that bupropion may reduce the abuse liability of methamphetamine. Confirmatory studies utilizing self-administration approaches would be useful to expand upon these findings. The impact of bupropion treatment on methamphetamine use outside of the laboratory (where much larger doses are used) can only be assessed in an outpatient clinical trial.

Bupropion treatment was associated with reduced cue-induced craving. The GCS was modeled on craving scales developed for craving for cocaine and smoking urges (Merikle, 1999; Tiffany and Drobes, 1991; Tiffany *et al*, 1993). Thus, the GCS captures more dimensions of craving than do visual analogue scales (Tiffany *et al*, 1993). In drug discrimination tests in pigeons and rats, bupropion substitutes for methamphetamine (Johanson and Barrett, 1993; Munzar and Goldberg, 2000; Sasaki *et al*, 1995). In addition, bupropion is self-administered intravenously (i.v.) by squirrel monkeys and baboons (Bergman *et al*, 1989; Lamb and Griffiths, 1990), indicating that i.v. bupropion produces reinforcing effects in non-human primates similar to that produced by commonly abused stimulants (cocaine, methamphetamine). Differences between the drugs emerge when bupropion and methamphetamine are administered together. Bupropion pretreatment antagonizes methamphetamine-induced stereotypy, but when administered following methamphetamine, bupropion treatment augments methamphetamine-induced stereotypy (Muley *et al*, 1984).

These disparate results can be explained by the known effects of bupropion on the DA transporter (DAT). In an *in vitro* model consisting of immortalized cells transfected with the human DAT, bupropion dose dependently inhibited DA reuptake (Eshleman *et al*, 1994). On the other hand, bupropion pretreatment has been shown to protect against acute methamphetamine-induced decreases in DA uptake in striatal synaptasomes (Kim *et al*, 2000). Similar effects have been reported *in vivo*, as bupropion pretreatment reduced the neurotoxic effects produced by a single large dose (100 mg/kg, s.c.) of methamphetamine in rats (Marek *et al*, 1990). These effects appear to be due to the ability of bupropion to inhibit the inward transport of methamphetamine, thus limiting the ability of methamphetamine to displace DA from vesicular stores. In a recent report (Rau *et al*, 2005), bupropion rapidly, reversibly, and dose dependently increased vesicular DA uptake, an effect associated with vesicular monoamine transporter-2 protein redistribution. Of interest, the bupropion-induced increases in vesicular DA uptake were prevented by pretreatment with eticlopride, a DA D_2 receptor antagonist, but not by SCH 23390, a DA D_1 receptor antagonist.

When administered alone, bupropion increases synaptic DA by inhibiting reuptake. When administered with methamphetamine, bupropion may reduce synaptic DA by reducing the ability of methamphetamine to induce DA release. Bupropion has been reported to produce agonist-like effects in acutely abstinent smokers (Shiffman *et al*, 2000). As such, reduced ratings on subjective effects measures in this study may have been the result of the ability of bupropion to inhibit methamphetamine-induced DA release.

Despite this information, DA may not be the sole neurotransmitter system mediating the effects produced by bupropion. For example, bupropion does not inhibit prolactin, which would be expected if it significantly increases central DA (Whiteman *et al*, 1983). Moreover, therapeutic doses of bupropion have been reported to produce just 25% occupancy of the DA transporter (Learned-Coughlin *et al*, 2003), which may be inadequate to account for alterations to methamphetamine-induced DA release (Dworkin *et al*, 1998). Finally, other data suggest that stimulants (including methamphetamine) release norepinepherine (NE) more potently than DA (Rothman *et al*, 2001), and this neurotransmitter system may be responsible for some of the subjective effects reported in the current study.

We also found that bupropion blocked cue-induced craving. Similar results were reported in smokers, as bupropion treatment was associated with reduced cigarette cue-induced craving (Brody *et al*, 2004). The observed effects may have been the result of inhibition of NE reuptake, resulting in increased extracellular NE, which in turn reduced NE cell firing (Dong and Blier, 2001). Reduced NE output would, in turn, produce reduced cue reactivity and associated changes in cerebral metabolic activity.

The findings in this report are subject to a range of limitations. While bupropion pretreatment reliably reduced some of the subjective effects produced by methamphetamine, the doses of methamphetamine used were small. Methamphetamine-addicted individuals typically use much greater amounts, and may be prone to overcome modest reductions produced by a given medication (eg bupropion). In fact, preclinical models of self-administration demonstrate that reductions in subjective or reinforcing effects are generally accompanied by an increase in the amount of drug administered. Of interest, group differences were not noted between the 15 and 30 mg doses of methamphetamine. A careful analysis of individual responses revealed that this was likely the result of the considerable variability between subjects. Specifically, some patients exhibited moderate to robust responses to methamphetamine exposure, while others show little or no response. When considering only the group means, the impression is that the doses produced equivalent effects (which underestimates the individual responses to the drug). An additional limitation of the current study is the use of low doses of methamaphetamine and an equally low dose of bupropion. The doses selected were chosen on the basis of safety information showing that higher doses of bupropion are associated with onset of seizures (Pesola and Avasarala, 2002). In addition, the Physicians Desk Reference website (www.pdr.net) specifies, 'Zyban is contraindicated in patients with a seizure disorder, Zyban is contraindicated in patients treated with Wellbutrin, Wellbutrin SR, Wellbutrin XL, or any other medications that contain bupropion because the incidence of seizure is dose dependent, and Zyban is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion'. Moreover, the PDR site specifies caution for the interactions of bupropion with stimulants. Specifically, 'Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin'. A final limitation worth noting is the short exposure regimen and small sample size, signaling the need to replicate and extend these findings in a larger cohort (ie in a Phase II clinical trial).

The finding that bupropion reduced cue-induced craving for methamphetamine is especially compelling, although in the absence of other measures of drug seeking behavior (such as self-administration) it is difficult to infer the consequences of reduced craving. Furthermore, based on research with cue exposure in cocaine users (Robbins *et al*, 1997), it is likely that not all methamphetamine users respond to cues with increased craving. Further research in more homogenous populations may facilitate identification of subgroups that would best respond to treatments that alter cue responsivity.

ACKNOWLEDGEMENTS

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METHAMPHETIME RESEARCH STUDY

PERSONAL SUMMARY

Ryan K

DEMOGRAPHICS OF STUDY:

NAME	Burpropion Reduces Methamphetamine induced subjective effects and cue induced cravings
DIRECTORY	
COUNTRY	United States
UNIVERSITY	Los Angeles University of California
STUDY START	2006
STUDY END	2006
# OF PEOPLE	26 people | 10 placebo | 10 Burpropion and 6 mixed study
DATE READ	12/26/2019

PRINCIPLE CONCLUSIONS:

Cravings were not significantly different between placebo and the and the control.

Study summarizes that it may be effective for light use but not for moderate to heavy users.

COMMENTS: